Nitrates, beta blockers, and calcium channel blockers are the mainstay of therapy for patients with chronic stable angina. Sublingual nitroglycerin is the therapy of choice in acute episodes for immediate relief of angina and for prevention of angina prior to engaging in strenuous physical activity. Chronic nitrate therapy with long-acting oral formulations (isosorbide dinitrate or mononitrate) is used to prevent recurrent anginal episodes in patients with chronic stable angina.

Sublingual nitroglycerin is absorbed rapidly from oral mucosa directly into the venous circulation and has a rapid onset of action within 2-5 minutes. Long-acting **isosorbide dinitrate** is absorbed via the gastrointestinal tract and undergoes **extensive first-pass metabolism** in the liver prior to release in the systemic circulation. This leads to **low bioavailability** and the need for much higher doses of oral formulations as compared to sublingual nitroglycerin.

**(Choice A)** Chronic nitrate therapy on a regular basis leads to nitrate tolerance, with attenuation of blood pressure response and anti-anginal effects. Higher doses do not prevent nitrate tolerance. On the contrary, use of sublingual nitroglycerin on an intermittent, as-needed basis (nitrate-free intervals) prevents the development of nitrate tolerance.

**(Choices C and D)** The oral nitrate preparations do not have high serum protein binding or volume of distribution.

**(Choice E)** Isosorbide dinitrate has rapid and nearly complete intestinal absorption. Its low bioavailability is due to considerable first-pass hepatic metabolism.

**Educational objective:**
Isosorbide dinitrate has a low bioavailability due to extensive first-pass hepatic metabolism prior to release in systemic circulation. Sublingual nitroglycerin is absorbed directly from oral mucosa into the venous circulation and has a higher bioavailability.

**References**

- Clinical pharmacokinetics of nitrates

A 71-year-old man with chronic stable angina comes to the office for routine follow-up. He has occasional episodes of chest pain that improve after taking sublingual nitroglycerin. The patient also has a history of hypertension and hypercholesterolemia and takes multiple medications for his conditions. Blood pressure is 140/80 mm Hg and pulse is 68/min and regular. Examination reveals normal heart sounds. While discussing a plan to start isosorbide dinitrate therapy, the patient becomes concerned about the high dose of oral isosorbide dinitrate compared to sublingual nitroglycerin. Which of the following is the most likely reason for using a high dose of oral nitrate?

- A. Drug tolerance prevention (6%)
- ✓ B. High first-pass metabolism (77%)
- C. High serum protein binding (2%)
- D. High volume of distribution (4%)
- E. Low intestinal absorption (8%)

Correct | 77% Answered correctly | 03 secs Time Spent | 2023 Version

Explanation

Nitrates, beta blockers, and calcium channel blockers are the mainstay of therapy for patients with chronic stable angina. Sublingual nitroglycerin is the therapy of choice in acute episodes for immediate relief of angina and for prevention of angina prior to engaging in strenuous physical activity. Chronic nitrate therapy with long-acting oral formulations (isosorbide dinitrate or mononitrate) is used to prevent recurrent anginal episodes in patients with chronic stable angina

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- A. Drug tolerance prevention
- B. High first-pass metabolism
- C. High serum protein binding
- D. High volume of distribution
- E. Low intestinal absorption

Submit

| | |
|---|---|
| Nonimmunologic | • Hemolysis with sulfa drugs (G6PD deficiency) |

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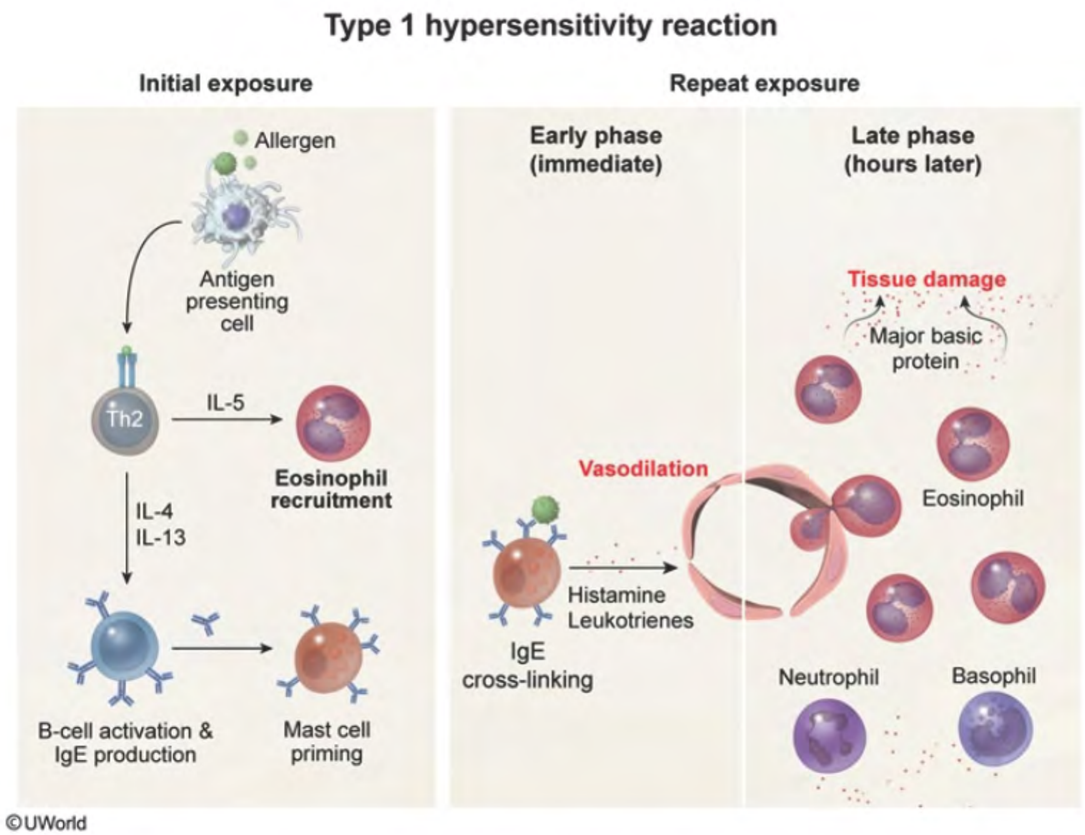


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treatment of syphilis or Lyme disease. It is not expected with the treatment of bacterial tonsillopharyngitis.

exposure to penicillin, this patient formed **specific IgE antibodies** to a beta-lactam-carrier protein antigen; these antibodies attached to the surface of mast cells and basophils, priming them for repeat exposure. On subsequent exposure to amoxicillin, a similar beta-lactam-carrier protein antigen is generated (ie, **repeat exposure**) that binds to surface-bound IgE to cause massive **mast cell degranulation** and widespread release of histamine and inflammatory mediators. An immediate allergic reaction is generated, resulting in urticarial rash (eg, erythema and wheals), bronchoconstriction with wheezing, or in severe cases, anaphylaxis.

**(Choice A)** Drug interactions occur when one drug facilitates an adverse effect of another, usually via impaired clearance. Probenecid inhibits the renal clearance of amoxicillin, leading to a higher risk of predictable amoxicillin adverse effects (eg, nausea).

**(Choice B)** Jarisch-Herxheimer reaction is a non-IgE–mediated immunologic hypersensitivity that involves fever, nonurticarial rash, and hypotension in response to a massive release of spirochetal antigens following antibiotic treatment of syphilis or Lyme disease. It is not expected with the treatment of bacterial tonsillopharyngitis.

**(Choice D)** Some drugs (eg, vancomycin, opioids), but not amoxicillin, can directly induce mast cell degranulation, causing urticarial rash and wheezing that closely mimics true type 1 hypersensitivity. This is a nonimmunologic, pseudoallergic reaction as it does not involve IgE.

**(Choice E)** Some drugs (eg, doxycycline) can react with ultraviolet light to cause a rash similar to sunburn. Amoxicillin is not associated with this type of nonimmunologic photosensitivity.

**Educational objective:**
Drugs (eg, beta-lactam antibiotics) and their metabolites can act as haptens that bind to a carrier protein to form antigens that generate an immunologic response. Type 1 hypersensitivity is IgE-mediated and involves a sensitization phase and a repeat exposure phase; clinical manifestations include urticarial rash, wheezing, and anaphylaxis.

Pharmacology  Pharmacology (General Principles)  Drug allergy

This patient with previous exposure to a **beta-lactam antibiotic** (ie, penicillin) developed an **urticarial rash within hours** of taking another beta-lactam antibiotic (ie, amoxicillin), likely due to IgE-mediated type 1 hypersensitivity. Most drug molecules are **too small** to elicit an immunologic response on their own, but some drugs or their metabolites can cause allergic hypersensitivity by acting as a **hapten** that binds to a **carrier protein** to form an immunogenic **foreign antigen**. Beta-lactams are commonly associated with this phenomenon.

Type 1 hypersensitivity involves a **sensitization phase** that takes place on initial exposure. During previous exposure to penicillin, this patient formed **specific IgE antibodies** to a beta-lactam-carrier protein antigen; these antibodies attached to the surface of mast cells and basophils, priming them for repeat exposure. On subsequent exposure to amoxicillin, a similar beta-lactam-carrier protein antigen is generated (ie, **repeat exposure**) that binds to surface-bound IgE to cause massive **mast cell degranulation** and widespread release of histamine and inflammatory mediators. An immediate allergic reaction is generated, resulting in urticarial rash (eg, erythema and wheals), bronchoconstriction with wheezing, or in severe cases, anaphylaxis.

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**Educational objective:**

| Drug adverse effects | | |
|---|---|---|
| **Predictable** | Pharmacologic | • Orthostatic hypotension with alpha-1 blockade<br>• Bradycardia with beta blockade<br>• Gastritis with cyclooxygenase inhibition<br>• Nausea with many drugs (numerous mechanisms) |
| | Secondary (indirect) | • Oral thrush or *Clostridioides difficile* colitis with antibiotics<br>• Phototoxicity with doxycycline |
| **Unpredictable*** | Immunologic | • Hypersensitivity (eg, anaphylaxis, serum sickness)<br>• Drug-induced lupus, SJS/TEN |
| | Nonimmunologic | • Flushing syndrome with vancomycin (pseudoallergy)<br>• Hemolysis with sulfa drugs (G6PD deficiency)<br>• Exaggerated azathioprine sensitivity (TPMT deficiency) |

* Unpredictable adverse effects are usually driven by patient-specific genetics or immunology.

**G6PD** = glucose-6-phosphate dehydrogenase; **SJS/TEN** = Stevens-Johnson syndrome/toxic epidermal necrolysis; **TPMT** = thiopurine methyltransferase.

This patient with previous exposure to a **beta-lactam antibiotic** (ie, penicillin) developed an **urticarial rash within hours** of taking another beta-lactam antibiotic (ie, amoxicillin), likely due to IgE-mediated type 1 hypersensitivity. Most drug molecules are **too small** to elicit an immunologic response on their own, but some drugs or their metabolites can cause allergic hypersensitivity by acting as a **hapten** that binds to a **carrier protein** to form an immunogenic **foreign antigen**. Beta-lactams are commonly associated with this phenomenon.

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An 8-year-old boy returns to the emergency department due to a pruritic rash that began 30 minutes ago. Earlier in the day, he was diagnosed with acute tonsillopharyngitis and oral amoxicillin was prescribed. The patient has no known drug allergies and had received penicillin on one previous occasion. Vital signs are within normal limits. Physical examination shows urticaria on the extremities and torso. There is faint bilateral wheezing. Which of the following factors was most essential for the current adverse reaction to occur in this patient?

- A. Drug interaction with another concomitantly taken medication
- ✗ B. Extensive cytokine activation due to lysed bacteria
- ✓ C. Formation of hapten-carrier protein combination antigens
- D. Non-IgE-mediated spontaneous mast cell degranulation
- E. Reaction of ultraviolet light with drug deposited in the skin

Incorrect
Correct answer
C

Collecting Statistics

08 secs
Time Spent

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Version

Explanation

| Drug adverse effects | | |
|---|---|---|
| **Predictable** | Pharmacologic | • Orthostatic hypotension with alpha-1 blockade<br>• Bradycardia with beta blockade<br>• Gastritis with cyclooxygenase inhibition<br>• Nausea with many drugs (numerous mechanisms) |

An 8-year-old boy returns to the emergency department due to a pruritic rash that began 30 minutes ago. Earlier in the day, he was diagnosed with acute tonsillopharyngitis and oral amoxicillin was prescribed. The patient has no known drug allergies and had received penicillin on one previous occasion. Vital signs are within normal limits. Physical examination shows urticaria on the extremities and torso. There is faint bilateral wheezing. Which of the following factors was most essential for the current adverse reaction to occur in this patient?

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Submit

commonly used medications that should be avoided in the elderly include benzodiazepines (and other sedating medications), antipsychotics, many antiarrhythmics (eg, digoxin), and centrally acting skeletal muscle relaxants.

**(Choices A and E)** Although hypotension due to excessive antihypertension medication use could cause dizziness, this patient has normal blood pressure and heart rate, making this much less likely as a cause of her dizziness. In addition, although centrally acting alpha agonists (eg, clonidine) and alpha-1 blockers (eg, doxazosin) confer a high risk of orthostatic hypotension in elderly patients, thiazide diuretics (eg, hydrochlorothiazide), calcium channel blockers (eg, amlodipine), and ACE inhibitors/angiotensin II receptor blockers are generally considered acceptable for this population.

**(Choice B)** Aspirin should be used with caution in older adults due to the increased risk of gastric ulcer; however, the reduced risk of cardiovascular events provided by aspirin in patients with prior transient ischemic attack or stroke likely outweighs this risk.

**(Choice D)** Donepezil is a cholinesterase inhibitor that is commonly used in the treatment of Alzheimer dementia. Bradycardia can occasionally occur; however, this patient has a normal heart rate.

**(Choice F)** Selective serotonin reuptake inhibitors (eg, sertraline) are the preferred first-line medications for depression in older adults. Serotonin-norepinephrine reuptake inhibitors (eg, duloxetine) may also be used, especially for patients with chronic pain. Tricyclic antidepressants are relatively contraindicated in the elderly due to their anticholinergic effects.

**Educational objective:**
The Beers criteria identify drugs that should be used with caution in geriatric patients. Common drugs to avoid include anticholinergics (eg, first-generation antihistamines), centrally acting alpha-2 agonists, tricyclic antidepressants, benzodiazepines (and other sedating medications), antipsychotics, many antiarrhythmics (eg, digoxin), and skeletal muscle relaxants.

**References**

- American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults.

Older patients are at increased risk for adverse effects of medications due to decreased drug clearance, cognitive and sensory deficits, multiple comorbidities, drug-drug interactions, and poor drug compliance. **Polypharmacy** (ie, ≥5 prescription and/or over-the-counter medications) is of particular concern in the elderly and can lead to a prescribing cascade, in which additional drugs are given for adverse effects that are misinterpreted as a new medical condition.

The **Beers criteria** were developed to identify drugs requiring caution in geriatric patients. **First-generation antihistamines** (eg, diphenhydramine) and other drugs with anticholinergic activity can increase the risk of confusion, hallucinations, dizziness, dry mouth, and constipation and should be avoided in this population. Other commonly used medications that should be avoided in the elderly include benzodiazepines (and other sedating medications), antipsychotics, many antiarrhythmics (eg, digoxin), and centrally acting skeletal muscle relaxants.

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| Common medications to avoid in older adults (Beers criteria) | |
|---|---|
| **Anticholinergic** | • First-generation antihistamines<br>• Gastrointestinal antispasmodics |
| **Cardiovascular** | • Alpha-1 blockers (as antihypertensives)<br>• Centrally acting alpha-2 agonists<br>• Many antiarrhythmics |
| **CNS** | • Tricyclic antidepressants<br>• Antipsychotics<br>• Barbiturates, benzodiazepines & other hypnotics |
| **Endocrine** | • Long-acting sulfonylureas<br>• Sliding-scale insulin |
| **Pain** | • Nonselective NSAIDs<br>• Skeletal muscle relaxants |
| **NSAIDs** = nonsteroidal anti-inflammatory drugs. | |

Older patients are at increased risk for adverse effects of medications due to decreased drug clearance, cognitive and sensory deficits, multiple comorbidities, drug-drug interactions, and poor drug compliance. **Polypharmacy** (ie, ≥5 prescription and/or over-the-counter medications) is of particular concern in the elderly and can lead to a prescribing cascade, in which additional drugs are given for adverse effects that are misinterpreted as a new medical condition.

The **Beers criteria** were developed to identify drugs requiring caution in geriatric patients. **First-generation antihistamines** (eg, diphenhydramine) and other drugs with anticholinergic activity can increase the risk of confusion, hallucinations, dizziness, dry mouth, and constipation and should be avoided in this population. Other

An 82-year-old woman is brought to the office for a new patient evaluation. She recently moved in with her daughter. The patient reports frequent dizziness but cannot provide additional details regarding her symptoms. Medical history includes moderate dementia, hypertension, transient ischemic attack, depression, and chronic insomnia. Blood pressure is 124/72 mm Hg, and pulse is 66/min and regular. Neurologic examination shows disorientation to time and place but normal deep tendon reflexes and no focal sensory or motor deficits. The patient's medication schedule includes 12 different drugs that are used to manage her chronic conditions. Which of the following medications should be discontinued at this time?

- A. Amlodipine (6%)
- ✗ B. Aspirin (0%)
- ✓ C. Diphenhydramine (81%)
- D. Donepezil (3%)
- E. Hydrochlorothiazide (3%)
- F. Sertraline (3%)

Incorrect
Correct answer
C

81%
Answered correctly

04 secs
Time Spent

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Version

Explanation

| Common medications to avoid in older adults (Beers criteria) | |
|---|---|
| **Anticholinergic** | • First-generation antihistamines |

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Submit

At least 2 distinct COX-1-dependent mechanisms contribute to the increased risk of upper **gastrointestinal (GI) bleeding** associated with aspirin therapy: Inhibition of platelet aggregation and impairment of prostaglandin-dependent GI mucosal protection. The risk of upper GI bleeding increases with higher doses but is increased 2- to 3-fold even with low-dose aspirin. Proton pump inhibitors can help reduce the risk of upper GI bleeding in patients taking aspirin.

**(Choice A)** Central nervous system depression is commonly seen with benzodiazepine use as these agents potentiate the effect of GABA (a major inhibitory neurotransmitter) on GABA-A receptors.

**(Choice C)** Very high doses of aspirin can cause salicylism (eg, vertigo, tinnitus, hearing loss) and hyperpnea (stimulates respiratory drive). Hyperpnea may result in respiratory alkalosis, whereas systemic salicylate accumulation often leads to a concurrent metabolic acidosis.

**(Choice D)** Orthostatic hypotension may occur with use of antihypertensive medications due to vasodilation (eg, nitrates, calcium channel blockers) and volume depletion (eg, loop and thiazide diuretics).

**(Choice E)** Sexual dysfunction is a common side effect of antidepressants (eg, selective serotonin inhibitors, tricyclics) and some antihypertensives (eg, thiazide diuretics, spironolactone, clonidine).

**(Choice F)** Pioglitazone (a thiazolidinedione) increases insulin sensitivity in patients with type II diabetes mellitus by binding to peroxisome proliferator-activated receptors. Long-term use may be associated with urinary bladder cancer.

**Educational objective:**
Gastrointestinal (GI) mucosal injury and bleeding are the most common side effects of aspirin. These are due primarily to cyclooxygenase-1 inhibition, which results in impaired prostaglandin-dependent GI mucosal defense and decreased platelet aggregation.

**References**

- Long-term use of aspirin and the risk of gastrointestinal bleeding

This patient, with hypertension, hypercholesterolemia, and sudden-onset neurologic deficits (eg, right arm weakness, difficulty speaking) that fully resolved within minutes, most likely had a **transient ischemic attack** (TIA). In addition to optimal blood pressure control and statin therapy, **low-dose aspirin** is commonly used to **prevent ischemic stroke** in patients with TIA. It works by irreversibly acetylating/inhibiting the cyclooxygenase (COX) enzymes. At low doses, aspirin predominantly **inhibits COX-1**, preventing platelet synthesis of thromboxane A2, which **impairs platelet aggregation** and reduces vasoconstriction.

At least 2 distinct COX-1-dependent mechanisms contribute to the increased risk of upper **gastrointestinal (GI) bleeding** associated with aspirin therapy: Inhibition of platelet aggregation and impairment of prostaglandin-dependent GI mucosal protection. The risk of upper GI bleeding increases with higher doses but is increased 2- to 3-fold even with low-dose aspirin. Proton pump inhibitors can help reduce the risk of upper GI bleeding in patients taking aspirin.

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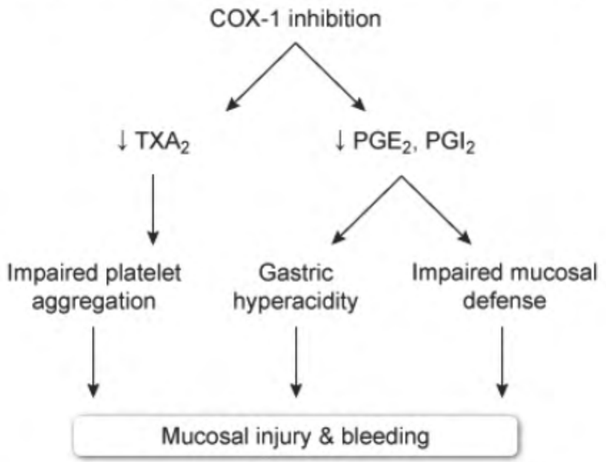
**(Choice F)** Pioglitazone (a thiazolidinedione) increases insulin sensitivity in patients with type II diabetes mellitus by binding to peroxisome proliferator-activated receptors. Long-term use may be associated with urinary bladder cancer.

E. Sexual dysfunction (2%)

Exhibit Display

**NSAID-induced gastrointestinal bleeding**




**COX-1** = cyclooxygenase 1; **NSAID** = nonsteroidal anti-inflammatory drug;
**$PGE_2$** = prostaglandin $E_2$; **$PGI_2$** = prostaglandin $I_2$ (prostacyclin);
**$TXA_2$** = thromboxane $A_2$.



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(TIA). In addition to optimal blood pressure control and statin therapy, **low-dose aspirin** is commonly used to

A 64-year-old woman comes to the hospital due to sudden-onset right arm weakness and difficulty speaking, which completely resolved within 20 minutes. The patient has had no shaking movements, headache, nausea, photophobia, or anxiety. She has a history of hypertension and hypercholesterolemia and takes amlodipine and rosuvastatin, respectively. Her blood pressure is 125/70 mm Hg and pulse is 78/min and regular. Neurologic examination is unremarkable. Fingerstick glucose is within normal limits. ECG shows normal sinus rhythm. Carotid Doppler reveals mild left common carotid artery stenosis. MRI of the brain and echocardiogram are unremarkable. If the patient is started on an additional medication that is indicated for her condition, which of the following adverse effects is most likely to occur?

- A. Central nervous system depression (2%)
- ✓ B. Gastrointestinal bleeding (63%)
- ✗ C. Hyperpnea and vertigo (2%)
- D. Orthostatic hypotension (28%)
- E. Sexual dysfunction (2%)
- F. Urinary bladder cancer (0%)

Incorrect
Correct answer
B

63%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

**NSAID-induced gastrointestinal bleeding**

COX-1 inhibition

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- B. Gastrointestinal bleeding
- C. Hyperpnea and vertigo
- D. Orthostatic hypotension
- E. Sexual dysfunction
- F. Urinary bladder cancer

Submit

This patient's new-onset hypertension and elevated levels of serum creatinine and cyclosporine are suggestive of acute **calcineurin inhibitor nephrotoxicity**. Calcineurin inhibitors such as cyclosporine cause dose-dependent renal vasoconstriction and tubular cell damage, which can precipitate acute renal failure.

Cyclosporine is extensively metabolized by the liver and gastrointestinal tract via the cytochrome P450 system, specifically the **CYP3A isoenzymes**. Inhibition of intestinal P450 enzymes by the furocoumarins present in **grapefruit juice** can slow the breakdown of drugs metabolized by this pathway, raising circulating levels of the affected drugs. Medications with a narrow therapeutic index (eg, cyclosporine) have the highest risk of toxicity.

**(Choice A)** Changes in gastric pH do not significantly affect the oral bioavailability of cyclosporine.

**(Choice C)** Transmembrane cyclosporine transport is not affected by grapefruit juice.

**(Choice D)** Pharmacodynamic potentiation is defined as a greater than additive effect that occurs when 2 different drugs are administered simultaneously due to functional interactions within the target tissues. Grapefruit juice increases the effect of cyclosporine by slowing its metabolism, which is a pharmacokinetic mechanism.

**(Choice E)** A decrease in plasma protein binding could lower the apparent volume of distribution of a fixed dose of cyclosporine, thereby increasing the amount of free drug in circulation. However, grapefruit juice does not influence the binding of cyclosporine to plasma proteins.

**Educational objective:**
Calcineurin inhibitor nephrotoxicity with resultant impairment of renal function is the most significant adverse effect of cyclosporine. Cytochrome P450 3A (CYP3A) is responsible for cyclosporine metabolism in the small intestine and liver. Grapefruit juice inhibits this enzyme and increases the nephrotoxicity of cyclosporine by raising circulating drug levels (pharmacokinetic interaction).

**References**

- The effect of grapefruit juice on cyclosporine and prednisone metabolism in transplant patients.

A 34-year-old kidney transplant patient treated with cyclosporine comes to the office due to nausea and anorexia. The patient underwent transplantation 6 months ago and had been doing well until recently. On examination, his blood pressure is 160/96 mm Hg. There is no tenderness at the site of the transplanted kidney. Serum creatinine is 3.4 mg/dL, and the serum cyclosporine level is markedly increased. A month ago, he had normal blood pressure and normal levels of cyclosporine and serum creatinine. Further questioning reveals that the patient has been drinking increased amounts of grapefruit juice lately as part of an attempt to improve his overall health. Which of the following mechanisms is most likely responsible for this patient's current condition?

- A. Alteration of gastric acidity (1%)
- ✓ B. Inhibition of cytochrome P450 enzymes in the gut wall (81%)
- ✗ C. Modification of transmembrane drug transport (2%)
- D. Pharmacodynamic potentiation (13%)
- E. Reduction of plasma protein binding (1%)

Incorrect
Correct answer
B

81%
Answered correctly

04 secs
Time Spent

2023
Version

## Explanation

This patient's new-onset hypertension and elevated levels of serum creatinine and cyclosporine are suggestive of acute **calcineurin inhibitor nephrotoxicity**. Calcineurin inhibitors such as cyclosporine cause dose-dependent renal vasoconstriction and tubular cell damage, which can precipitate acute renal failure.

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- D. Pharmacodynamic potentiation
- E. Reduction of plasma protein binding

Submit

effects (eg, nephrotoxicity, ototoxicity, myelosuppression) that occur due to accumulation within normal tissues (ie, off-t

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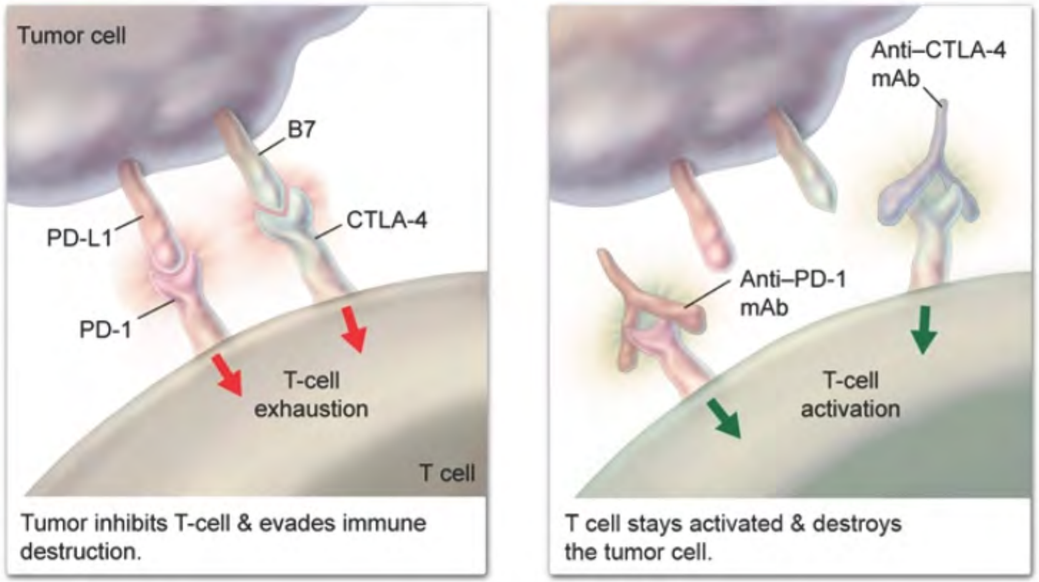
bevacizumab) bind VEGF and inhibit tumor-induced angiogenesis. Although EGFR stimulation also plays a role in angiogenesis, in this case, the anti-EGFR antibodies are used for targeting purposes and may not necessarily

Exhibit Display

**Cancer immunotherapy: anti–PD-1 & anti–CTLA-4 antibodies**




**CTLA-4** = cytotoxic T-lymphocyte–associated protein 4; **mAb** = monoclonal antibody;
**PD-1** = programmed death receptor-1; **PD-L1** = programmed death ligand-1.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**antibodies** on the liposome surface results in an **antibody-drug conjugate**, allowing the encapsulated drug complex to **selectively bind to tumor cells** expressing high levels of EGFR, which is often overexpressed in non–small cell lung cancer. Once bound, the antibody-drug complex is internalized and degraded, releasing the free drug into the cytoplasm and causing targeted cell death.

**(Choice A)** Overexpression of drug efflux pumps (eg, P-glycoprotein) by cancer cells is a major cause of chemotherapy resistance. Efflux pump inhibitors can decrease drug excretion from tumor cells and potentiate the effects of chemotherapeutic agents.

**(Choice B)** Many cancers create an immunosuppressive microenvironment that prevents the immune system from effectively killing tumor cells. An enhanced cytotoxic T-cell response against tumor cells occurs with the use of immune checkpoint inhibitors (eg, PD-1 or CTLA-4 receptor inhibitors) that help prevent T-cell exhaustion.

**(Choice C)** Desmoplasia (ie, reactive growth of fibrous connective tissue) occurs in response to certain tumors (eg, breast, pancreatic carcinoma). The dense fibrotic tissue acts as a molecular sieve, decreasing the penetration of chemotherapeutic agents. Chemoresistance is more likely to occur with larger drug complexes; in this case, the new liposomal formulation will be much larger than individual cisplatin molecules, resulting in decreased desmoplastic penetration.

**(Choice D)** Increased expression of vascular endothelial growth factor (VEGF) within tumors stimulates blood vessel growth, facilitating tumor expansion and increasing the potential for metastasis. Anti-VEGF antibodies (eg, bevacizumab) bind VEGF and inhibit tumor-induced angiogenesis. Although EGFR stimulation also plays a role in angiogenesis, in this case, the anti-EGFR antibodies are used for targeting purposes and may not necessarily inhibit the EGFR receptor (antibodies can be stimulatory, inhibitory, or have no signaling effect depending on the attachment site).

**Educational objective:**
Antibody-drug conjugates improve drug efficacy and minimize toxicity by allowing conventional chemotherapeutic agents (eg, cisplatin) to selectively target and kill cancer cells while sparing healthy cells (ie, targeted delivery).

*EGFR is frequently overexpressed in lung cancer, breast cancer, and glioblastoma.


Platinum-based chemotherapy agents (eg, cisplatin) are widely used as a first-line treatment for many solid tumors, including non–small cell lung cancer. These agents disrupt DNA replication and have substantial cytotoxicity against rapidly proliferating cells. Despite their efficacy in killing tumor cells, their use is limited by severe adverse effects (eg, nephrotoxicity, ototoxicity, myelosuppression) that occur due to accumulation within normal tissues (ie, off-target effects).

Methods that provide **targeted delivery** to the tumor site can help **minimize toxicity** and **optimize drug response**. In this example, cisplatin is encapsulated in liposomes, forming a nanoparticle cage that traps the drug and limits its interaction with normal cells. The addition of anti–epidermal growth factor receptor **(anti-EGFR) antibodies** on the liposome surface results in an **antibody-drug conjugate**, allowing the encapsulated drug complex to **selectively bind to tumor cells** expressing high levels of EGFR, which is often overexpressed in non–small cell lung cancer. Once bound, the antibody-drug complex is internalized and degraded, releasing the free drug into the cytoplasm and causing targeted cell death.

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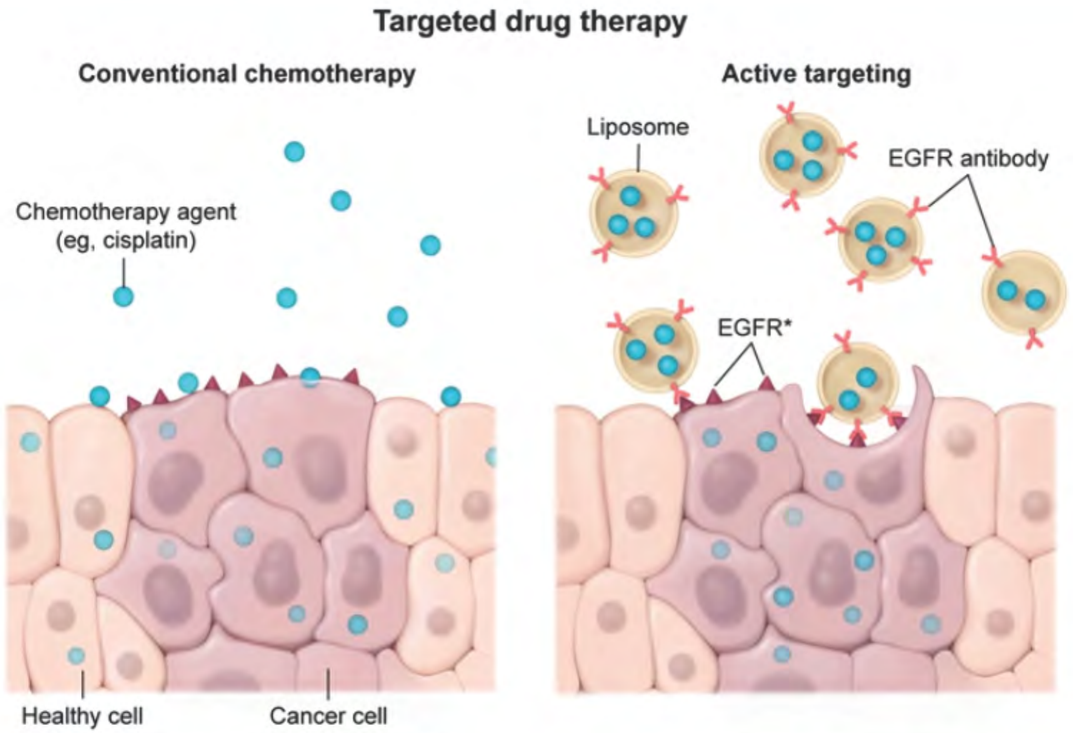


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(eg, cisplatin)

A clinical trial is conducted to assess the effectiveness of a novel formulation of cisplatin for treating advanced non–small cell lung cancer. Study participants are randomly assigned to 2 different cisplatin-based chemotherapy regimens. Subjects in the control arm are administered conventional cisplatin chemotherapy, whereas those in the experimental arm are given a formulation of cisplatin encapsulated in liposomes coated with anti–epidermal growth factor receptor (EGFR) antibodies. Patients in the experimental group are found to have a statistically significant decrease in residual tumor burden compared with those in the control group. The incidence of adverse effects was also lower in the experimental group. Compared to conventional cisplatin chemotherapy, the new formulation is most likely to have which of the following effects?

- A. Decreased drug efflux from tumor cells (5%)
- ✕ B. Enhanced cytotoxic T-cell response (5%)
- C. Increased penetration through dense desmoplasia (9%)
- D. Inhibition of tumor-induced angiogenesis (31%)
- ✓ E. Selective drug uptake by cancer cells (48%)

Incorrect
Correct answer
E

48%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

A clinical trial is conducted to assess the effectiveness of a novel formulation of cisplatin for treating advanced non–small cell lung cancer. Study participants are randomly assigned to 2 different cisplatin-based chemotherapy regimens. Subjects in the control arm are administered conventional cisplatin chemotherapy, whereas those in the experimental arm are given a formulation of cisplatin encapsulated in liposomes coated with anti–epidermal growth factor receptor (EGFR) antibodies. Patients in the experimental group are found to have a statistically significant decrease in residual tumor burden compared with those in the control group. The incidence of adverse effects was also lower in the experimental group. Compared to conventional cisplatin chemotherapy, the new formulation is most likely to have which of the following effects?

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* Unpredictable adverse effects are usually driven by patient-specific genetics or immunology.

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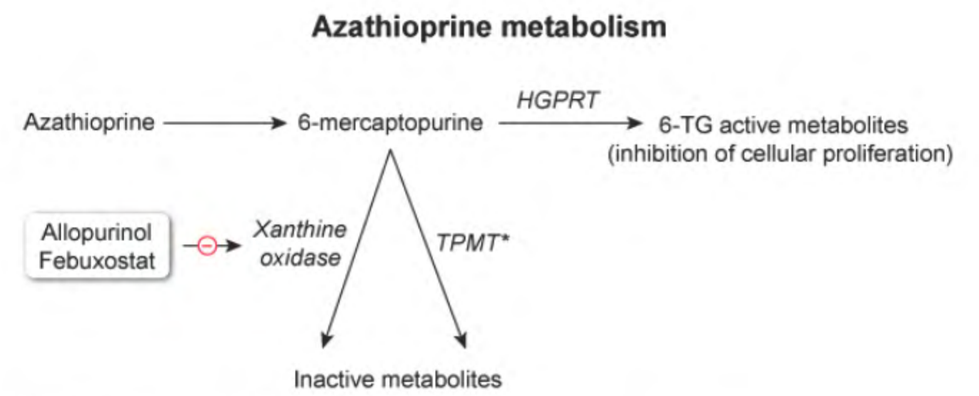


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can lead to oxidative cellular injury and nonimmune hemolytic anemia.

Nonimmunologic
- Flushing syndrome with vancomycin (pseudoallergy)
- Hemolysis with sulfa drugs (G6PD deficiency)

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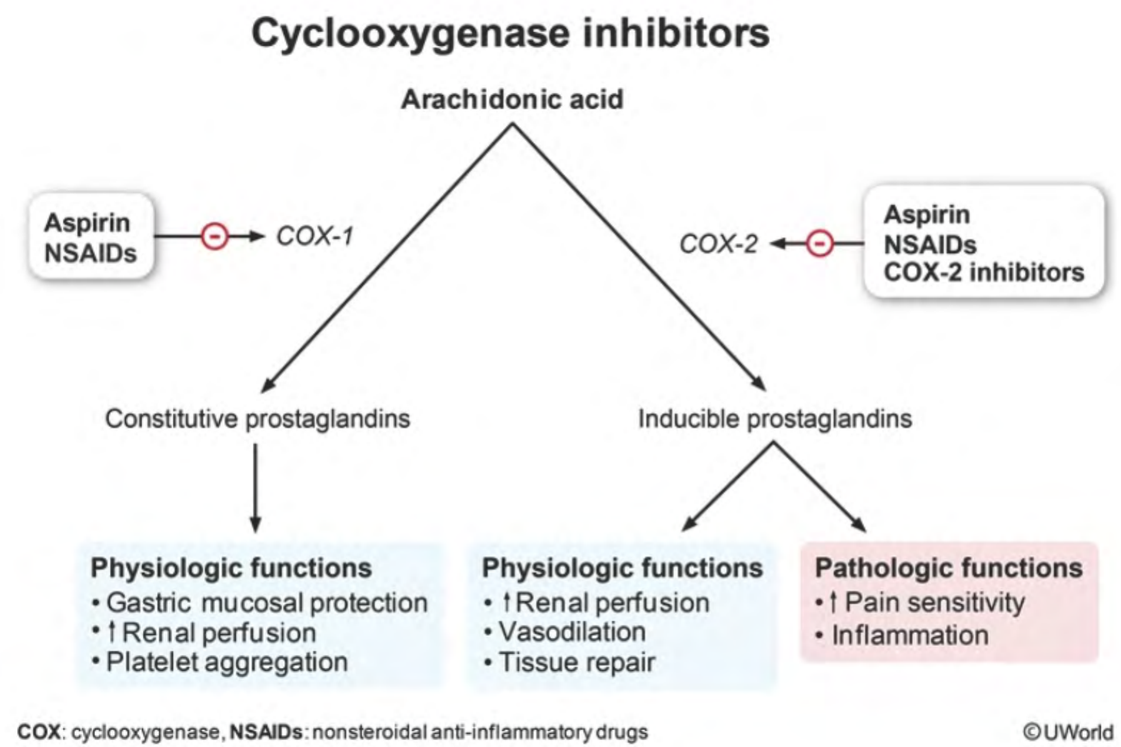


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**(Choice B)** An idiosyncratic drug reaction is an unpredictable reaction (ie, results from patient-specific

Most adverse drug reactions are **predictable** due to the **known pharmacologic properties** of the drug, and often occur after extended drug exposure. Unpredictable reactions are less common and occur due to relatively patient-specific immunologic processes or other mechanisms (eg, genetic enzyme deficiencies). In this case, upper gastrointestinal bleeding due to an NSAID is a well-known and predictable adverse effect.

**(Choice A)** Exaggerated drug sensitivity, also sometimes called drug intolerance, refers to an unpredictable reaction that occurs due to a known pharmacologic action of the drug but at a lower dose than expected (likely due to patient-specific alterations in metabolism or end-organ susceptibility). For example, patients with deficiency of thiopurine methyltransferase, an enzyme that metabolizes azathioprine, are more likely to experience azathioprine intolerance.

**(Choice B)** An idiosyncratic drug reaction is an unpredictable reaction (ie, results from patient-specific complexities) that does not involve a typical pharmacologic action of the drug. For example, the use of the antibiotic trimethoprim-sulfamethoxazole in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency can lead to oxidative cellular injury and nonimmune hemolytic anemia.

**(Choice C)** Immunologic drug reactions (drug allergies) are unpredictable antibody-or T cell-mediated responses to medications. This patient's history of rash and pruritus with penicillin likely represents IgE-mediated type I hypersensitivity.

**(Choice E)** Pseudoallergic drug reactions mimic immunologic reactions but occur via a nonimmunologic mechanism (eg, direct immune cell activation) in those with patient-specific susceptibility. Vancomycin, opioids, and radioiodine contrast can directly activate mast cells to cause a pseudoallergic reaction that closely mimics IgE-mediated type I hypersensitivity.

**Educational objective:**
Most adverse drug reactions are predictable and result from known pharmacologic properties of the drug. Unpredictable reactions are less common and are typically driven by patient-specific genetics (eg, enzyme deficiency) or immunologic mechanisms.

This patient has **upper gastrointestinal hemorrhage**, which is likely an **adverse effect** of the nonsteroidal anti-inflammatory drug (**NSAID**) he has been taking. Cyclooxygenase (COX) catalyzes the rate-limiting step in the conversion of arachidonic acid to prostaglandins, prostacyclin, and thromboxane. COX enzymes are involved in mediating inflammation but are also required for housekeeping functions such as platelet aggregation, renal protection, and gastric mucosal protection. Inhibition of COX enzymes by NSAIDs (eg, naproxen, ibuprofen) leads to **impaired** prostaglandin-dependent **gastric mucosal protection** and the potential development of gastritis (ie, erythema, erosions) and ulceration. Changes to the gastric mucosa may be seen within the first week of initiating NSAID therapy.

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| Drug adverse effects | | |
|---|---|---|
| **Predictable** | Pharmacologic | • Orthostatic hypotension with alpha-1 blockade<br>• Bradycardia with beta blockade<br>• Gastritis with cyclooxygenase inhibition<br>• Nausea with many drugs (numerous mechanisms) |
| | Secondary (indirect) | • Oral thrush or *Clostridioides difficile* colitis with antibiotics<br>• Phototoxicity with doxycycline |
| **Unpredictable*** | Immunologic | • Hypersensitivity (eg, anaphylaxis, serum sickness)<br>• Drug-induced lupus, SJS/TEN |
| | Nonimmunologic | • Flushing syndrome with vancomycin (pseudoallergy)<br>• Hemolysis with sulfa drugs (G6PD deficiency)<br>• Exaggerated azathioprine sensitivity (TPMT deficiency) |

* Unpredictable adverse effects are usually driven by patient-specific genetics or immunology.

**G6PD** = glucose-6-phosphate dehydrogenase; **SJS/TEN** = Stevens-Johnson syndrome/toxic epidermal necrolysis; **TPMT** = thiopurine methyltransferase.

This patient has **upper gastrointestinal hemorrhage**, which is likely an **adverse effect** of the nonsteroidal anti-inflammatory drug (**NSAID**) he has been taking. Cyclooxygenase (COX) catalyzes the rate-limiting step in the conversion of arachidonic acid to prostaglandins, prostacyclin, and thromboxane. COX enzymes are involved in mediating inflammation but are also required for housekeeping functions such as platelet aggregation, renal protection, and gastric mucosal protection. Inhibition of COX enzymes by NSAIDs (eg, naproxen, ibuprofen) leads to **impaired** prostaglandin-dependent **gastric mucosal protection** and the potential development of gastritis (ie, erythema, erosions) and ulceration. Changes to the gastric mucosa may be seen within the first week of initiating NSAID therapy.

A 35-year-old man comes to the emergency department due to acute onset coffee-ground emesis and lightheadedness. Two months ago, he developed lower back pain with stiffness and began taking naproxen and cyclobenzaprine. Medical history is notable for moderate persistent asthma, hepatitis C, and HIV. His last CD4 count was 550/mm$^3$. The patient has a remote history of intravenous drug use but currently does not use any recreational drugs. He has an allergy to penicillin that causes a rash and pruritus. Upper gastrointestinal endoscopy reveals gastric mucosal erythema and erosions. Which of the following best explains this patient's current symptoms?

- A. Exaggerated drug sensitivity
- B. Idiosyncratic drug reaction
- C. Immunologic drug reaction
- ✓ D. Predictable drug reaction
- ✗ E. Pseudoallergic drug reaction

Incorrect
Correct answer
D

Collecting Statistics

50 secs
Time Spent

2023
Version

Explanation

| Drug adverse effects | | |
|---|---|---|
| | Pharmacologic | • Orthostatic hypotension with alpha-1 blockade<br>• Bradycardia with beta blockade<br>• Gastritis with cyclooxygenase inhibition |

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Submit

**SNRI** = serotonin-norepinephrine reuptake inhibitor; **SSRI** = selective serotonin reuptake inhibitor; **TCA** = tricyclic antidepressant.

**Serotonin syndrome** is characterized by a triad of **autonomic instability** (eg, hyperthermia, hypertension, tachycardia), **altered mental status** (eg, agitation, confusion), and **neuromuscular hyperactivity** (eg, tremor, hyperreflexia, myoclonus), as well as gastrointestinal symptoms and diaphoresis. It is due to an increased serotonergic effect in the central nervous system (eg, increased 5-HT1A and 5-HT2A receptor stimulation).

Serotonin syndrome rarely occurs with a single serotonergic drug used at therapeutic doses. More commonly, it is due to the combined effects of several serotonergic medications, overdose, and/or a drug-drug interaction. Serotonin effect is increased when a **monoamine oxidase inhibitor** (MAOI) is **combined** with a **serotonergic antidepressant** (selective serotonin reuptake inhibitor [SSRI], serotonin-norepinephrine reuptake inhibitor, or tricyclic antidepressant).

Linezolid is used to treat infections caused by gram-positive bacteria, particularly vancomycin-resistant enterococcus and methicillin-resistant *Staphylococcus aureus*. **Linezolid has MAOI activity** and therefore can precipitate serotonin syndrome with concomitant use of an SSRI (eg, paroxetine) or with other serotonergic medications.

**(Choices A, B, D, and E)** Clindamycin, doxycycline, penicillin, and vancomycin do not have MAOI effects. They do not cause serotonin syndrome when combined with a serotonergic antidepressant.

**Educational objective:**
Serotonin syndrome is characterized by a triad of autonomic instability, altered mental status, and neuromuscular irritability. It may develop when a monoamine oxidase inhibitor (MAOI) antidepressant or a non-antidepressant with MAOI activity (eg, linezolid) is combined with a serotonergic medication such as a selective serotonin reuptake inhibitor, serotonin-norepinephrine reuptake inhibitor, or tricyclic antidepressant.

**References**

| Serotonin syndrome | |
|---|---|
| **Causes** | • Serotonergic medications, especially in combination (eg, SSRI/SNRI, TCA, tramadol)<br>• Drug interactions: Serotonergic medication & MAOI or linezolid<br>• Intentional overdose of serotonergic medications<br>• Serotonergic drugs of abuse (eg, MDMA) |
| **Clinical features** | • Mental status changes (eg, anxiety, agitation, delirium)<br>• Autonomic dysregulation (eg, diaphoresis, hypertension, tachycardia, hyperthermia, vomiting, diarrhea)<br>• Neuromuscular hyperactivity (eg, tremor, myoclonus, hyperreflexia) |
| **MAOI** = monoamine oxidase inhibitor; **MDMA** = 3,4-Methylenedioxymethamphetamine; **SNRI** = serotonin-norepinephrine reuptake inhibitor; **SSRI** = selective serotonin reuptake inhibitor; **TCA** = tricyclic antidepressant. | |

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A 52-year-old woman comes to the emergency department due to recurrent right lower extremity swelling, pain, and erythema. The patient's medical history includes type 2 diabetes mellitus and depression. Her medications include metformin, paroxetine, and a multivitamin. The patient is diagnosed with cellulitis, admitted to the hospital, and started on antibiotics. She is continued on her home medications. Three days later, the patient becomes agitated and delirious with severe abdominal cramps and diarrhea. Her temperature is 39.2 C (102.6 F), blood pressure is 180/100 mm Hg, and heart rate is 120/min and regular. On examination, the patient is diaphoretic and tremulous, and her pupils are dilated. Bilateral hyperreflexia and ankle clonus are present. She begins to have seizures. Which of the following antibiotics was the patient most likely given to treat the cellulitis?

- A. Clindamycin (16%)
- ✗ B. Doxycycline (8%)
- ✓ C. Linezolid (58%)
- D. Penicillin (6%)
- E. Vancomycin (10%)

Incorrect
Correct answer
C

58%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

| Serotonin syndrome | |
|---|---|
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- C. Linezolid
- D. Penicillin
- E. Vancomycin

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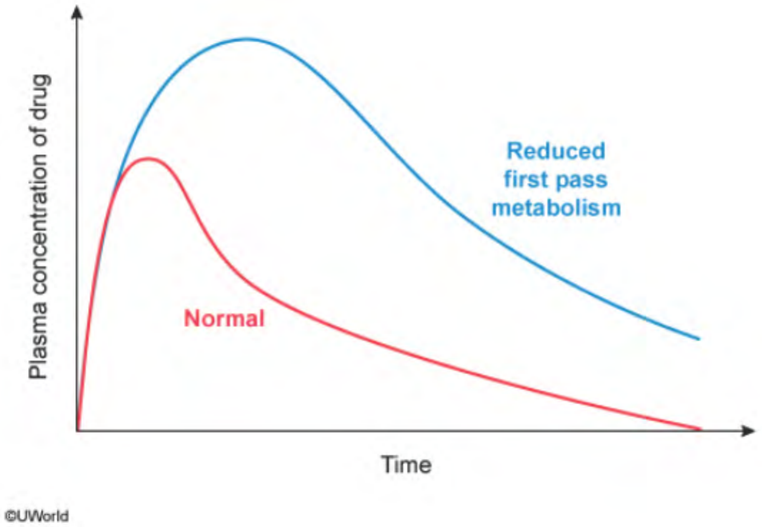


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Pharmacology (General Principles) | Route of administration & bioavailability
Subject | System | Topic

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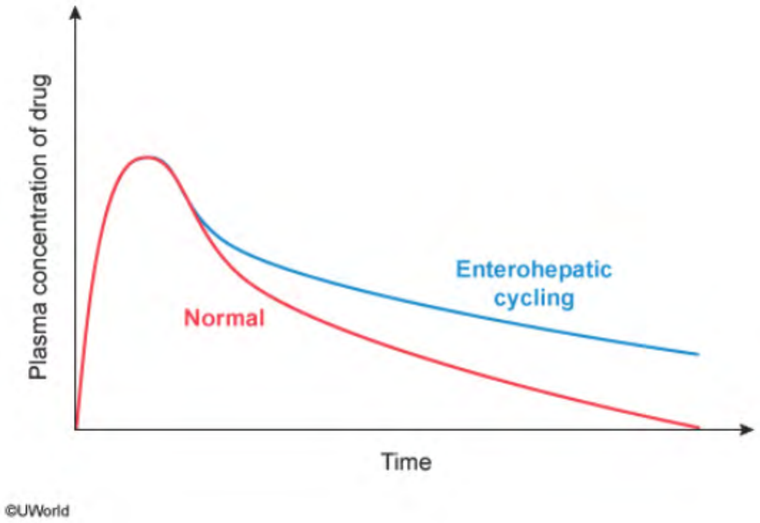


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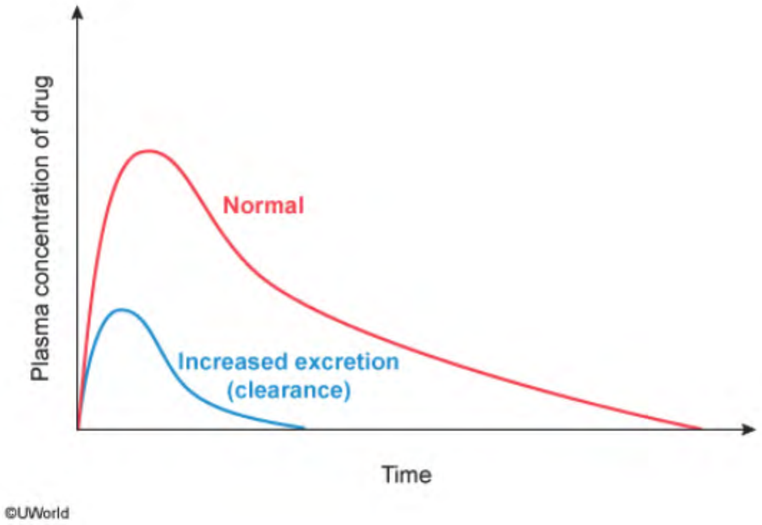


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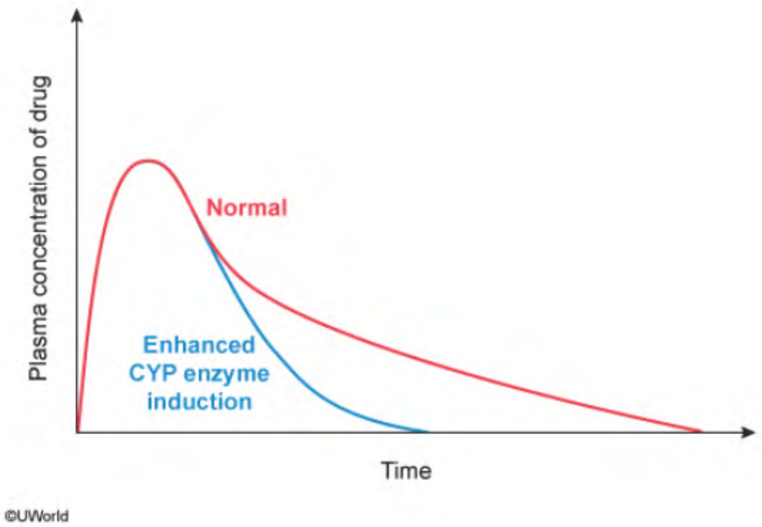


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encapsulated with coatings that dissolve at different rates to **delay intestinal absorption**. Slower drug absorption can have several advantages, including:

- Reduced incidence of adverse effects due to dampening of peak levels
- Longer duration of therapeutic effect due to prolonged absorption of the drug
- Improved patient compliance due to less frequent administration

These benefits make sustained-release preparations particularly useful for drugs with short half-lives (ie, allowing prolonged effect without need for multiple doses) or narrow therapeutic windows (ie, maintaining effective drug levels while minimizing absorption peaks).

**(Choice B)** Enhanced CYP enzyme induction by the blue formulation would cause increased drug metabolism over time as additional enzymes are synthesized, leading to decreased serum drug levels.

**(Choice C)** Increased biliary excretion of the blue formulation would be expected to decrease peak serum levels, but would not explain the delay in peak levels relative to the red curve.

**(Choice D)** Drugs that are excreted into the bile can undergo enterohepatic cycling, which can prolong the drug's effect longer than expected given the drug's half-life. However, increased enterohepatic cycling would not explain the initial delay in peak serum levels seen in the blue curve.

**(Choice E)** Reduced first-pass metabolism by the blue formulation would result in higher peak serum levels compared to the red curve due to increased quantities of drug entering the circulation.

**Educational objective:**
Sustained-release drug preparations have reduced and delayed peak levels compared to immediate-release preparations due to slower absorption in the gastrointestinal tract. Dampening of peak levels and prolonged absorption of the drug help maintain effective drug levels while minimizing toxicity.

| Pharmacology | Pharmacology (General Principles) | Route of administration & bioavailability |
|---|---|---|
| Subject | System | Topic |

The above graph shows the plasma drug concentration-time curves of the 2 different oral formulations. The one represented by the blue curve shows a **reduced and delayed peak** level relative to the red curve, which is consistent with a **sustained-release preparation**.

The absorption speed of an orally administered drug depends on the rate at which it dissolves in gastrointestinal fluids. Capsules and tablets can be designed with the active ingredient embedded in an insoluble matrix or encapsulated with coatings that dissolve at different rates to **delay intestinal absorption**. Slower drug absorption can have several advantages, including:

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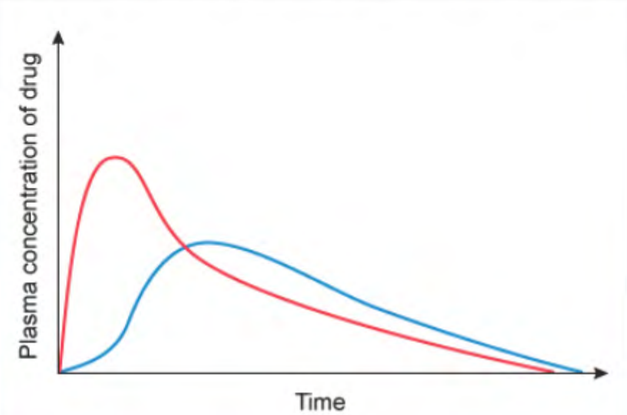
**Educational objective:**

A pharmaceutical company in the final stages of designing a new nonsteroidal anti-inflammatory agent develops 2 different oral formulations of the drug. Two groups of volunteers are each administered a different formulation, and average plasma drug levels are monitored over the next 12 hours. The results are shown below:




Compared to the red curve, the formulation represented by the blue curve is most likely to have which of the following characteristics?

- ✓ A. Delayed intestinal absorption (68%)
- ✗ B. Enhanced CYP enzyme induction (7%)
- C. Increased biliary excretion (2%)
- D. Increased enterohepatic cycling (8%)
- E. Reduced first-pass metabolism (13%)

Incorrect
Correct answer
A

68%
Answered correctly

03 secs
Time Spent

2023
Version

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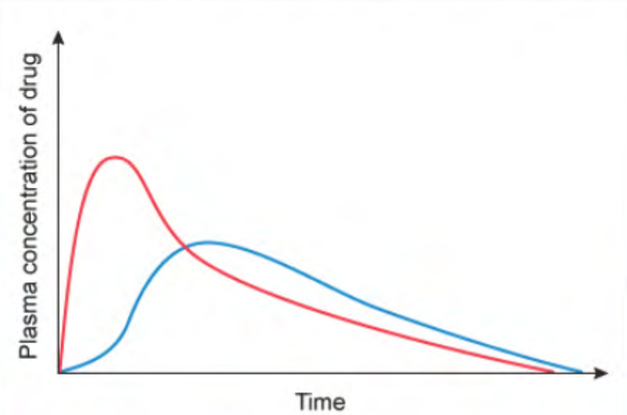


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- C. Increased biliary excretion
- D. Increased enterohepatic cycling
- E. Reduced first-pass metabolism

Submit

Statins, primarily simvastatin, lovastatin, and atorvastatin, are metabolized by **CYP3A4**. This enzyme can be **inhibited by macrolide antibiotics** (eg, erythromycin, clarithromycin), leading to increased statin drug levels and subsequent statin myopathy. (Azithromycin does not significantly inhibit CYP3A4.) Other significant CYP3A4 inhibitors that can induce statin myopathy include ketoconazole, non–dihydropyridine calcium channel blockers (eg, diltiazem), amiodarone, and protease inhibitors (eg, ritonavir). Because pravastatin is not primarily metabolized by CYP3A4, patients who must take a CYP3A4 inhibitor may benefit from switching to this drug.

**(Choice A)** Amoxicillin does not inhibit CYP3A4 or increase circulating simvastatin levels. Penicillin antibiotics generally have only minor effects on the cytochrome P-450 system.

**(Choice B)** Bismuth subsalicylate can cause black stools due to the formation of bismuth sulfate in the gastrointestinal tract. However, this medication does not cause myopathy or myoglobinuria. Excessive intake of bismuth can cause motor weakness, but this is due primarily to neural rather than muscle toxicity.

**(Choice C)** Polyvalent cations (eg, calcium, iron) can form insoluble chelate complexes with certain antibiotics (eg, tetracyclines, fluoroquinolones) and other drugs (eg, levothyroxine, levodopa), leading to decreased drug absorption. Simvastatin does not form chelate complexes, and decreased absorption would lower, not increase, the risk for myopathy.

**(Choice E)** Both metronidazole and simvastatin carry a small risk for peripheral neuropathy. In some patients, the effect can be additive and lead to numbness, pain, and paresthesia in the hands and feet. However, this neuropathy would not cause muscle tenderness or myoglobinuria.

**Educational objective:**
Statins, primarily simvastatin, lovastatin, and atorvastatin, are metabolized by CYP3A4. Drugs that inhibit this enzyme (eg, macrolide antibiotics, ketoconazole, non–dihydropyridine calcium channel blockers, amiodarone) can cause increased statin drug levels and lead to statin myopathy.

**References**

- Clinical guidance for managing statin and antimicrobial drug-drug interactions

This patient has muscle tenderness and weakness. The dark urine suggests **myoglobinuria** due to myocyte necrosis. In the context of ongoing statin therapy for hyperlipidemia, this presentation likely represents statin myopathy. Statin myopathy is due, likely at least in part, to decreased myocyte production of coenzyme Q10 (ubiquinone). Serum muscle breakdown markers (eg, creatine kinase) are often elevated, and severe cases may lead to **rhabdomyolysis** with subsequent **acute kidney injury** (eg, elevated BUN and creatinine).

**Statin myopathy** is most common in the initial weeks or months of therapy. However, it can occasionally occur later, and can be acutely triggered by medications that increase circulating statin levels. This patient's myopathy is most likely related to the initiation of clarithromycin as part of a multidrug regimen for *Helicobacter pylori*.

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| Concurrent medications & statin myopathy | |
|---|---|
| **Cytochrome P-450 (CYP3A4) inhibitors** | • Non–dihydropyridine CCBs (eg, verapamil, diltiazem)<br>• Protease inhibitors (eg, ritonavir, saquinavir)<br>• Erythromycin |
| **OATP inhibitors** | • Cyclosporine (also a CYP3A4 inhibitor) |
| **Additive myocyte toxicity** | • Corticosteroids<br>• Fibrates (eg, gemfibrozil)<br>• Colchicine (also competes with statins for CYP3A4 metabolism) |
| **CCBs** = calcium channel blockers; **OATP** = organic anion transport protein. | |

This patient has muscle tenderness and weakness. The dark urine suggests **myoglobinuria** due to myocyte necrosis. In the context of ongoing statin therapy for hyperlipidemia, this presentation likely represents statin myopathy. Statin myopathy is due, likely at least in part, to decreased myocyte production of coenzyme Q10 (ubiquinone). Serum muscle breakdown markers (eg, creatine kinase) are often elevated, and severe cases may lead to **rhabdomyolysis** with subsequent **acute kidney injury** (eg, elevated BUN and creatinine).

**Statin myopathy** is most common in the initial weeks or months of therapy. However, it can occasionally occur later, and can be acutely triggered by medications that increase circulating statin levels. This patient's myopathy is most likely related to the initiation of clarithromycin as part of a multidrug regimen for *Helicobacter pylori*.

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A 47-year-old man comes to the office due to worsening muscle weakness and dark urine for the past several days. Two weeks ago, the patient was evaluated for dyspepsia and found to have *Helicobacter pylori* infection; he was started on treatment and has had partial symptom improvement. Medical history includes hypertension and hyperlipidemia, for which he takes amlodipine and simvastatin. Temperature is 37.1 C (98.8 F), blood pressure is 130/80 mm Hg, and pulse is 74/min. Physical examination shows diffuse muscle tenderness. Laboratory evaluation reveals elevated blood urea nitrogen and serum creatinine levels. Urine microscopy shows no red or white blood cells. Which of the following medications most likely precipitated this patient's current condition?

- A. Amoxicillin (20%)
- ✗ B. Bismuth subsalicylate (9%)
- C. Calcium carbonate (5%)
- ✓ D. Clarithromycin (51%)
- E. Metronidazole (12%)

Incorrect
Correct answer
D

51%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

| Concurrent medications & statin myopathy | |
|---|---|
| **Cytochrome P-450 (CYP3A4) inhibitors** | • Non–dihydropyridine CCBs (eg, verapamil, diltiazem)<br>• Protease inhibitors (eg, ritonavir, saquinavir)<br>• Erythromycin |

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- C. Calcium carbonate
- D. Clarithromycin
- E. Metronidazole

Submit

target tissues  Therefore, drugs that bind their receptors with a higher affinity or are better able to gain access to their target tissues will have greater potency. The potency of different agents can be compared by determining the dose of drug that is required to produce one-half (50%) of the maximum biological response. This dose is known as the $ED_{50}$. The lower the $ED_{50}$ of a drug, the more potent it is. For example, among the thiazide diuretics, 25mg of hydrochlorothiazide and 5mg chlorthalidone produce similar drops in blood pressure (similar efficacy), but chlorthalidone requires a lower dose, or lower $ED_{50}$, than HCTZ to cause a similar effect (higher potency).

With respect to the question, drug 2 and drug 3 have similar maximum effects (efficacy). A much lower dose of drug 2 is required to produce the same effect as that seen with drug 3; therefore, drug 2 is more potent than drug 3 and has a lower $ED_{50}$. To achieve this higher potency, the binding of drug 2 to its receptors (affinity) must be higher than that of drug 3 **(Choice B)**, or drug 2 must be better able to reach its target (penetration) than drug 3.

**(Choice A)** Drug 1 has higher potency than Drug 2 because at low biological activity, it can cause the same effect with much lower concentrations of drug. However, it does not reach the same maximum effect as Drug 2.

**(Choice C)** Drug 1 demonstrates the lowest efficacy (ceiling of biological effect) of the three drugs graphed. Lower efficacy may be a result of partial agonism and other factors.

**(Choice D)** Drugs 2 and 3 exhibit a parallel shift in their relative biological effects exhibiting similar efficacy but different potency (The shapes of their graphs are identical, but at different dose ranges). Drug 3 may contain the same basic pharmocologic agent as Drug 2 but with a competitive antagonist mixed in; thus, the $E_{max}$ is the same but the $ED_{50}$ is higher. A competitive antagonist would bind to the same location as the original substance.

**(Choice E)** Drug 2 has a lower $ED_{50}$ (greater potency) than drug 3. Both have equal efficacy.

**Educational Objective:**
Efficacy is a measure of the maximum pharmacodynamic effect achievable with a drug. Potency refers to the dose of drug that is required to produce a given effect. Drugs that bind their receptors with a higher affinity or are better able to gain access to their target tissues will have greater potency (lower $ED_{50}$).

Explanation

Efficacy and potency are terms that are commonly used and often confused. In pharmacology, efficacy refers to the intrinsic ability of a drug to elicit an effect, such as receptor activation or dilation of a vessel as described in the question stem. It is a measure of the maximum ceiling of activity [$E_{max}$] of a drug with respect to a particular pharmacodynamic end point. For example, loop diuretics such as furosemide or bumetanide will cause greater diuresis or natriuresis than any thiazide diuretic, irrespective of dose.

Potency, on the other hand, refers to the dose of drug that is required to produce a given effect. The potency of a drug is primarily affected by the affinity of the drug for its receptor and the amount of drug that is able to reach the target tissues Therefore, drugs that bind their receptors with a higher affinity or are better able to gain access to their target tissues will have greater potency. The potency of different agents can be compared by determining the dose of drug that is required to produce one-half (50%) of the maximum biological response. This dose is known as the $ED_{50}$. The lower the $ED_{50}$ of a drug, the more potent it is. For example, among the thiazide diuretics, 25mg of hydrochlorothiazide and 5mg chlorthalidone produce similar drops in blood pressure (similar efficacy), but chlorthalidone requires a lower dose, or lower $ED_{50}$, than HCTZ to cause a similar effect (higher potency).

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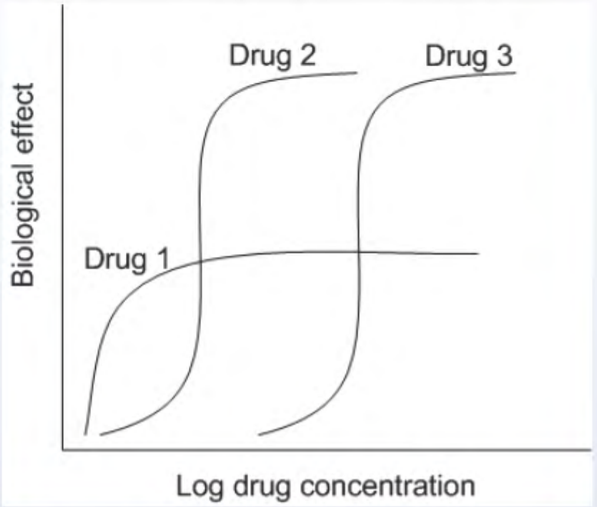
Three alpha-agonist drugs are tested as potential vasoconstrictors. The degree of vasoconstriction is determined by measuring the cross-sectional area of an isolated vessel after application of the drug. The following curves are obtained:




Which of the following is the best statement concerning the effects of these drugs?

- A. Drug 1 has lower potency than Drug 2 (6%)
- ✓ B. Drug 2 has higher affinity for alpha-receptors than Drug 3 (76%)
- C. Drug 1 demonstrates the highest efficacy (4%)
- D. Drug 2 and Drug 3 bind to different loci of alpha-receptors (5%)
- E. Drug 2 and Drug 3 demonstrate a similar potency (7%)

Correct

76% Answered correctly

03 secs Time Spent

2023 Version

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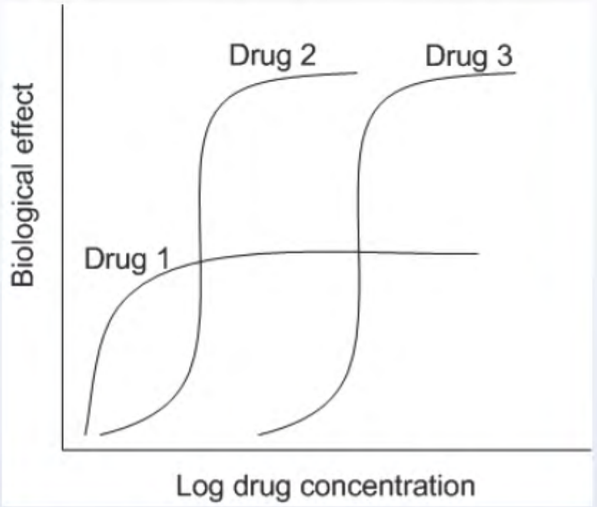


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Submit

Statins (eg, atorvastatin) are the first-line therapy for most patients with hypercholesterolemia and are useful in prim
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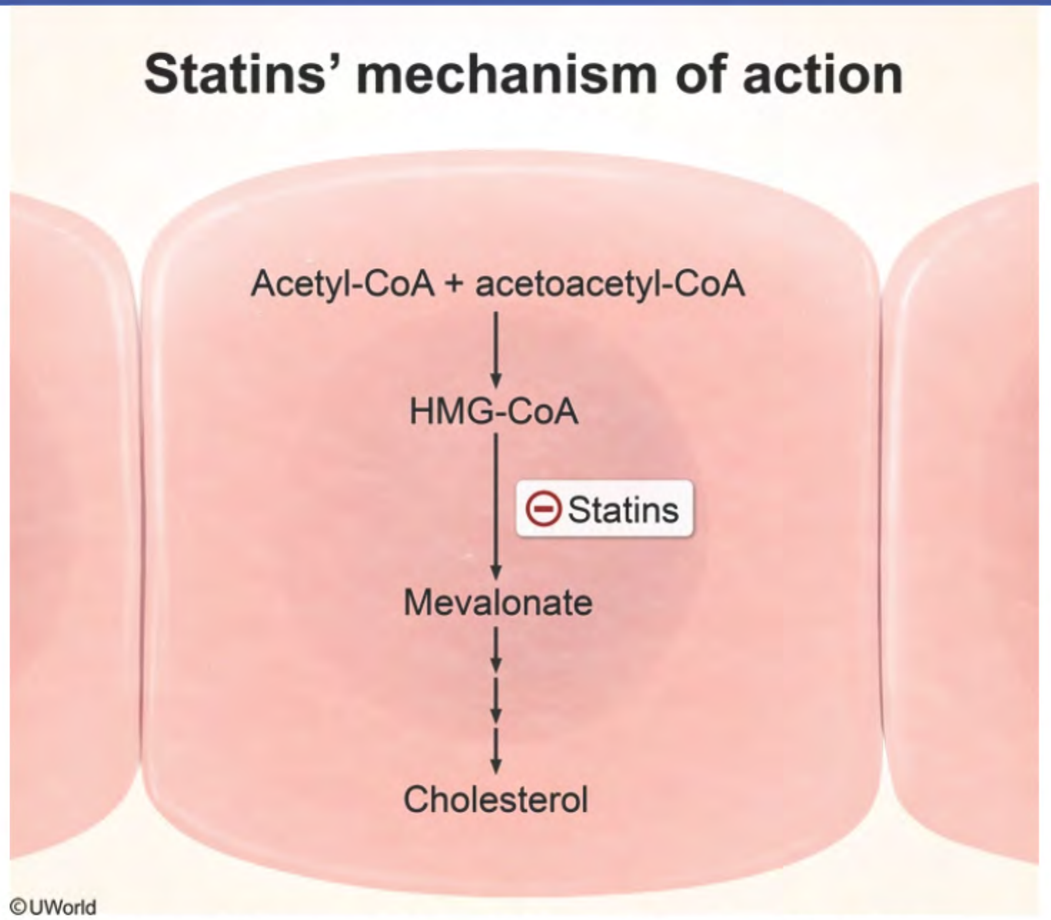


Zoom In | Zoom Out | Reset | New | Existing | My Notebook

Pharmacology | Pharmacology (General Principles) | Drug-induced myopathy

Statins (eg, atorvastatin) are the first-line therapy for most patients with hypercholesterolemia and are useful in primary and secondary prevention of acute coronary events. Statins inhibit HMG-CoA reductase, the enzyme responsible for the rate-limiting step in synthesis of cholesterol. Statins lower total cholesterol, LDL, and triglyceride levels.

The primary side effects of statins include myopathy and hepatitis. **Statin-associated myopathy** is usually characterized by mild muscular pain and resolves with discontinuation of the medication. However, some patients will develop severe myopathy with striking elevations in creatine kinase levels and occasional rhabdomyolysis. The risk of severe myopathy is increased when statins are given concurrently with fibrates (particularly **gemfibrozil**), which impair the hepatic clearance of statins and lead to excessive blood levels. An increased risk of statin myopathy is also likely with concurrent use of niacin or ezetimibe, but to a lesser extent **(Choice B)**.

**(Choice A)** Concurrent use of bile acid sequestrants (eg, cholestyramine) with statins does not increase the risk of myopathy. However, bile acid sequestrants can reduce the gastrointestinal absorption of statins.

**(Choice D)** Fibrates can increase drug levels of ezetimibe but this does not have a significant impact on its side effects, which are generally mild and not dose-related. Ezetimibe does not alter the pharmacokinetics of fibrates and does not substantially influence their adverse effects.

**(Choices E and F)** The primary adverse effects of niacin include flushing, hyperglycemia, and hepatotoxicity. There are no significant interactions with the concurrent use of niacin and ezetimibe or gemfibrozil.

**Educational objective:**
The primary side effects of statins include myopathy and hepatitis. Fibrates such as gemfibrozil can impair hepatic clearance of statins, increasing the risk of severe myopathy.

**References**

- Effect of gemfibrozil and fenofibrate on the pharmacokinetics of atorvastatin.

Pharmacology  Pharmacology (General Principles)  Drug-induced myopathy

A 68-year-old man comes to the office with a 6-week history of muscle pain and fatigue. He has achy pain that is not related to activity. The patient has tried warm compresses and over-the-counter analgesics without relief. Past medical history is significant for hypertension, mixed hyperlipidemia, and coronary artery disease with an acute myocardial infarction 2 years ago. Physical examination shows diffuse tenderness in the proximal muscles of the upper and lower extremities. Serum creatine kinase activity is elevated. Which of the following drug combinations is most likely responsible for this patient's condition?

- A. Atorvastatin and cholestyramine (7%)
- ✗ B. Atorvastatin and ezetimibe (10%)
- ✓ C. Atorvastatin and gemfibrozil (76%)
- D. Gemfibrozil and ezetimibe (1%)
- E. Niacin and ezetimibe (1%)
- F. Niacin and gemfibrozil (2%)

Incorrect
Correct answer
C

76%
Answered correctly

04 secs
Time Spent

2023
Version

Explanation

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- D. Gemfibrozil and ezetimibe
- E. Niacin and ezetimibe
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Submit

available to replace the deficient enzyme. Almost all human enzymes, including lysosomal enzymes, are large polypeptides (eg, proteins) **(Choice B)**. Although the oral route is often preferred for drug administration, most peptide-based drugs (eg, insulin, immunoglobulins) cannot be efficiently absorbed by the gastrointestinal tract due to the intestinal epithelial barrier and extensive proteolysis that takes place in the stomach and duodenum. As a result, **large polypeptides** such as a glucocerebrosidase must be **administered intravenously** to achieve adequate circulating levels.

Once in the circulation, exogenous glucocerebrosidase can enter cells by binding to **mannose 6-phosphate receptors**. These receptors are found in the Golgi network, where they help route newly synthesized lysosomal proteins (tagged by mannose 6-phosphate residues). They are also expressed **on the cell surface**, where they bind free lysosomal enzymes that are accidentally secreted. Exogenous glucocerebrosidase can bind to these cell surface receptors, inducing **endocytosis** of the bound enzyme. It is then carried by endosomes to lysosomes, where it can degrade accumulated glucocerebrosides, reducing disease manifestations.

**(Choices C and D)** Enzymes are large, polar polypeptides that are unable to effectively cross the cell membrane by passive diffusion. In contrast, steroid-based drugs are typically hydrophobic and can easily cross cell membranes by passive diffusion. However, steroidal drugs function by binding to receptors; they do not directly catalyze reactions.

**(Choices E, F, G, and H)** Unlike in lysosomal storage diseases, enzyme replacement therapy for pancreatic exocrine insufficiency is administered orally because pancreatic digestive enzymes normally function within the gastrointestinal lumen.

**Educational objective:**
Certain lysosomal storage diseases, including Gaucher disease, can be treated with enzyme-replacement therapy (eg, recombinant glucocerebrosidase). Because enzymes are large proteins that cannot be orally absorbed, the replacement enzyme must be administered intravenously. Entry into the cell occurs by endocytosis after the replacement enzyme binds to mannose 6-phosphate receptors on the cell surface.

This patient has **Gaucher disease**, an autosomal recessive condition caused by a **deficiency of lysosomal beta-glucocerebrosidase**. This deficiency leads to the accumulation of glucocerebroside, a glycolipid component of cell membranes, within the lysosomes of macrophages, giving them the classic appearance of wrinkled tissue paper. Characteristic symptoms (eg, hepatosplenomegaly, pancytopenia, bone pain) develop as lipid-laden macrophages accumulate in the body's tissues (eg, spleen, liver, and bone).

Lysosomal storage diseases can be treated through the delivery of a **replacement enzyme** into the lysosomes of affected cells; in the case of Gaucher disease, **recombinant glucocerebrosidases** (eg, imiglucerase) are available to replace the deficient enzyme. Almost all human enzymes, including lysosomal enzymes, are large polypeptides (eg, proteins) **(Choice B)**. Although the oral route is often preferred for drug administration, most peptide-based drugs (eg, insulin, immunoglobulins) cannot be efficiently absorbed by the gastrointestinal tract due to the intestinal epithelial barrier and extensive proteolysis that takes place in the stomach and duodenum. As a result, **large polypeptides** such as a glucocerebrosidase must be **administered intravenously** to achieve adequate circulating levels.

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examination, height and weight are at the 5th percentile for age. The abdomen is soft and nontender with the liver palpable 4 cm below the right costal margin and the spleen palpable 8 cm below the left costal margin. Laboratory results show anemia and thrombocytopenia. A bone marrow biopsy shows macrophages with wrinkled, paperlike cytoplasm due to the accumulation of glycolipids within lysosomes. The patient is prescribed enzyme replacement therapy. Which of the following sets of pharmacologic properties best characterizes the administered medication?

| | | Route of administration | Entry into target cells | Structure | |
|---|---|---|---|---|---|
| ✓ | A. | Intravenous | Endocytosis | Protein | (58%) |
| | B. | Intravenous | Endocytosis | Steroid | (5%) |
| | C. | Intravenous | Passive diffusion | Protein | (6%) |
| ✗ | D. | Intravenous | Passive diffusion | Steroid | (7%) |
| | E. | Oral | Endocytosis | Protein | (14%) |
| | F. | Oral | Endocytosis | Steroid | (2%) |
| | G. | Oral | Passive diffusion | Protein | (2%) |
| | H. | Oral | Passive diffusion | Steroid | (2%) |

Incorrect
Correct answer
A

58%
Answered correctly

07 secs
Time Spent

2023
Version

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| ○ D. | Intravenous | Passive diffusion | Steroid |
| ○ E. | Oral | Endocytosis | Protein |
| ○ F. | Oral | Endocytosis | Steroid |
| ○ G. | Oral | Passive diffusion | Protein |
| ○ H. | Oral | Passive diffusion | Steroid |

Submit

An 8-year-old boy is brought to the office due to fatigue and intermittent bone pain for the past year. The patient's parents are concerned because he has stopped playing outside and mostly stays indoors watching television. On examination, height and weight are at the 5th percentile for age. The abdomen is soft and nontender with the liver palpable 4 cm below the right costal margin and the spleen palpable 8 cm below the left costal margin. Laboratory results show anemia and thrombocytopenia. A bone marrow biopsy shows macrophages with wrinkled, paperlike cytoplasm due to the accumulation of glycolipids within lysosomes. The patient is prescribed enzyme replacement therapy. Which of the following sets of pharmacologic properties best characterizes the administered medication?

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|---|---|---|---|
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| ○ D. | Intravenous | Passive diffusion | Steroid |
| ○ E. | Oral | Endocytosis | Protein |
| ○ F. | Oral | Endocytosis | Steroid |
| ○ G. | Oral | Passive diffusion | Protein |
| ○ H. | Oral | Passive diffusion | Steroid |

30 minutes following administration (to avoid reflux of gastric contents).

Bisphosphonates are also associated with **osteonecrosis of the jaw** (mandible or maxilla) and atypical bone fractures (eg, stress fractures of the subtrochanteric zone and femoral shaft). The precise pathophysiology is debated and may vary, but proposed mechanisms include suppression of bone remodeling, impaired healing of microfractures, and decreased angiogenesis.

**(Choice A)** Medication-induced nephropathy can be due to interstitial nephritis (eg, cyclosporine), crystal nephropathy (eg, acyclovir), renal vasoconstriction (eg, amphotericin B, nonsteroidal anti-inflammatory drugs), or tubular injury (eg, aminoglycosides). Bisphosphonates are eliminated by the kidney and should be used with caution in patients with chronic kidney disease, but do not have substantial nephrotoxicity.

**(Choice B)** Bisphosphonates decrease bone resorption, thus lowering serum calcium levels. They are sometimes used in the treatment of severe hypercalcemia (eg, hypercalcemia of malignancy).

**(Choice D)** Venous thromboembolism is a recognized complication of selective estrogen receptor modulators (eg, raloxifene), but these medications do not often cause esophagitis. Bisphosphonates do not appreciably increase the risk of thromboembolism.

**(Choice E)** Vitamin $B_{12}$ deficiency can be seen in long-term proton pump inhibitor (eg, omeprazole) therapy, possibly due to decreased acid-dependent cleavage of vitamin $B_{12}$ from dietary proteins. Although proton pump inhibitors may be taken by patients with bisphosphonate-induced esophagitis, bisphosphonates do not affect vitamin $B_{12}$ metabolism.

**Educational objective:**
Medication-induced esophagitis is a common adverse effect of bisphosphonates. Bisphosphonates are also associated with increased risk of osteonecrosis of the jaw and atypical femoral fractures.

| Pharmacology | Pharmacology (General Principles) | Osteoporosis |
|---|---|---|
| Subject | System | Topic |

| Medication-induced esophagitis | |
|---|---|
| **Drug class** | **Drug** |
| Antibiotics | Tetracyclines |
| Anti-inflammatory agents | Aspirin & many nonsteroidal anti-inflammatory drugs |
| Bisphosphonates | Alendronate, risedronate |
| Others | Potassium chloride, iron |

This patient has esophagitis, with burning pain in the chest and dysphagia. **Medication-induced esophagitis** is a common adverse effect of **bisphosphonates** (eg, alendronate, risedronate) thought to be caused by disruption of the protective phospholipid barrier in the lower esophagus. This allows refluxing gastric acid to cause mucosal erosion and ulceration. Bisphosphonates are contraindicated in conditions that impair esophageal motility (eg, stricture, achalasia). When bisphosphonates are used, the risk of esophagitis can be lessened by taking the medication with a full glass of water (to ensure the pill is delivered fully into the stomach) and remaining upright for 30 minutes following administration (to avoid reflux of gastric contents).

Bisphosphonates are also associated with **osteonecrosis of the jaw** (mandible or maxilla) and atypical bone fractures (eg, stress fractures of the subtrochanteric zone and femoral shaft). The precise pathophysiology is debated and may vary, but proposed mechanisms include suppression of bone remodeling, impaired healing of microfractures, and decreased angiogenesis.

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A 68-year-old woman comes to the office due to a burning sensation in her chest and throat for the past 2 weeks. Associated symptoms include trouble swallowing. Medical history is significant for osteoporosis, and she has no known drug allergies. The patient has smoked half a pack of cigarettes daily for 50 years, and does not use alcohol or illicit drugs. Temperature is 36.7 C (98 F), blood pressure is 110/70 mm Hg, and pulse is 70/min. BMI is 20 kg/m$^2$. Cardiopulmonary examination shows clear lungs and normal S1 and S2. The abdomen is soft and nontender. Laboratory results are normal. It is determined that the patient's current symptoms are caused by one of her medications, which is discontinued. Her symptoms subsequently resolve. The medication responsible for this patient's presentation is also associated with which of the following side effects?

- A. Chronic kidney disease (5%)
- B. Hypercalcemia (10%)
- ✓ C. Osteonecrosis of the jaw (78%)
- D. Venous thromboembolism (4%)
- E. Vitamin $B_{12}$ deficiency (2%)

Correct

78%
Answered correctly

03 secs
Time Spent

2023
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Explanation

| Medication-induced esophagitis | |
|---|---|
| **Drug class** | **Drug** |

A 68-year-old woman comes to the office due to a burning sensation in her chest and throat for the past 2 weeks. Associated symptoms include trouble swallowing. Medical history is significant for osteoporosis, and she has no known drug allergies. The patient has smoked half a pack of cigarettes daily for 50 years, and does not use alcohol or illicit drugs. Temperature is 36.7 C (98 F), blood pressure is 110/70 mm Hg, and pulse is 70/min. BMI is 20 kg/m$^2$. Cardiopulmonary examination shows clear lungs and normal S1 and S2. The abdomen is soft and nontender. Laboratory results are normal. It is determined that the patient's current symptoms are caused by one of her medications, which is discontinued. Her symptoms subsequently resolve. The medication responsible for this patient's presentation is also associated with which of the following side effects?

- A. Chronic kidney disease
- B. Hypercalcemia
- C. Osteonecrosis of the jaw
- D. Venous thromboembolism
- E. Vitamin $B_{12}$ deficiency

Submit

capillary endothelial cells. P-glycoprotein is an ATP-driven **efflux pump** that actively **removes a wide range of substrates** from cells, including many commonly prescribed drugs (eg, antibiotics, immunosuppressant agents, HIV protease inhibitors).

In HIV infection, poor penetration of antiretroviral medications allows the brain to act as an anatomical sanctuary where viral replication can proceed unchecked, facilitating the development of resistant strains. Methods of bypassing the BBB (eg, disruption of tight junctions, **p-glycoprotein inhibition**) can **improve drug delivery** to the CNS. P-glycoprotein transporters are also found on the apical surface of enterocytes and can limit drug bioavailability by pumping the drug back into the intestinal lumen. However, inhibition of p-glycoprotein can have a **variable effect on serum drug levels**, as increased bioavailability is often countered by increased drug distribution (eg, into the CSF or intracellular compartments).

**(Choices A, B, and E)** Reduced drug metabolism or decreased excretion could potentially improve drug efficacy by increasing average serum drug levels. However, in this experiment, serum drug levels increased by only 10 ng/ml (~2%) with coadministration of the adjuvant. This minimal increase in drug concentration is not representative of a significant change in drug metabolic/clearance parameters and is unlikely to lead to increased BBB penetration.

**(Choice C)** The choroid plexus is the site of CSF production and can function as an alternate entryway into the CNS. However, the excretion of a substance by the choroid plexus is directly dependent on choroidal blood flow; diminished blood flow would reduce the excretion of a particular substance into the CSF.

**Educational objective:**
P-glycoprotein is an efflux pump found on brain capillary endothelial cells (part of the blood-brain barrier) that inhibits a wide range of substrates from entering the brain. Inhibition of p-glycoprotein can improve drug delivery to the CNS.

| Pharmacology | Pharmacology (General Principles) | Volume of distribution |
|---|---|---|
| Subject | System | Topic |

Explanation

The study results show that the cerebral spinal fluid (CSF) viral load level remains elevated when subjects are treated with Drug X alone but becomes undetectable when Drug X is combined with the adjuvant agent. Because average serum levels are relatively equal between the 2 groups, it is likely that the adjuvant improves the efficacy of Drug X by increasing its ability to penetrate the **blood-brain barrier** (BBB).

Many drugs have a difficult time crossing the BBB due to the presence of specialized endothelial cells with very **tight intercellular junctions** that form a **physical barrier** separating the CNS from the circulation. In addition, multidrug transport proteins, particularly **p-glycoprotein**, are highly expressed on the luminal membrane of brain capillary endothelial cells. P-glycoprotein is an ATP-driven **efflux pump** that actively **removes a wide range of substrates** from cells, including many commonly prescribed drugs (eg, antibiotics, immunosuppressant agents, HIV protease inhibitors).

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A novel antiretroviral medication, Drug X, is being developed for treating patients with HIV infection. Initial studies show a high rate of treatment failure due to continued viral proliferation in the brain. However, treatment success rates improve when Drug X is combined with an adjuvant agent. Data comparing the two medication regimens is shown in the table below.

| | Drug X only | Drug X + adjuvant |
|---|---|---|
| **Average cerebral spinal fluid (CSF) viral load (1 month)** | 1860 copies/mL | 480 copies/mL |
| **Average CSF viral load (6 months)** | 1640 copies/mL | undetectable |
| **Average serum concentration of Drug X** | 550 ng/ml | 560 ng/ml |

Based on the data, the adjuvant agent most likely improves viral control through which of the following mechanisms?

- A. Blocking first-pass metabolism (9%)
- ✗ B. Decreasing cytochrome P450 metabolism (19%)
- C. Diminishing blood flow to the choroid plexus (15%)
- ✓ D. Inhibiting cellular efflux transporters (50%)
- E. Reducing glomerular filtration of the drug (4%)

Incorrect
Correct answer
D

50%
Answered correctly

04 secs
Time Spent

2023
Version

Explanation

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Submit

of total body water. Within the extracellular fluid, the plasma volume is about 3 L, and interstitial fluid makes up the rest. Initially, the drug enters the plasma compartment by the IV route. If a drug has a large molecular weight, is bound extensively to plasma proteins, or is highly charged (hydrophilic), then the drug generally remains in the plasma compartment and the volume of distribution is usually low as in the case above (about 3-5 liters). If the drug has a small molecular weight but is hydrophilic, it can distribute into the interstitial fluid compartment outside of the blood vessels as well as in the intravascular compartment. In these cases the volume of distribution is limited to a total volume of about 14-16 liters (plasma volume plus interstitial volume). If the drug has a small molecular weight and is also uncharged (hydrophobic or lipophilic), then the drug can cross cell membranes and reach intracellular compartment. These drugs have the highest volume of distribution (41 liters). Drugs that are avidly bound in the tissues exhibit the highest volumes of distribution, often much higher than the total body water volume, because these drugs accumulate readily within cells thereby maintaining low plasma concentrations.

**(Choice A)** If the molecular weight of the drug is low, then the drug will tend to easily pass through endothelial junctions into the interstitial fluid, making the volume of distribution at least 14 liters. The Vd may be higher if the drug is also hydrophobic.

**(Choice B)** Lipophilic drugs tend to readily cross cell membranes and distribute widely outside the plasma and interstitial compartments. This tendency to collect within cells gives these drugs a high volume of distribution.

**(Choice C)** A drug with a $V_d$ of 4.5 L, which is approximately the same as the plasma volume, is likely to be highly bound to plasma proteins such as albumin. Binding to plasma proteins tends to retain drug in the plasma compartment and prevent the diffusion of drug into the extravascular compartments. If this drug were not bound to albumin, it would be more likely to diffuse into the interstitium and a higher $V_d$ would be expected.

**(Choice E)** Bioavailability is a measure of absorption and is unrelated to the distribution of a drug.

**Educational Objective:**
Characteristics of a drug such as high molecular weight, high plasma protein binding, high charge, and hydrophilicity tend to trap the drug in the plasma compartment resulting in a low $V_d$ (3-5 L).

Explanation

The volume of distribution ($V_d$) refers to a hypothetical volume of fluid into which the administered amount of drug would need to be uniformly distributed to produce the observed plasma concentration. The volume of distribution is determined by administering a given amount of drug by the intravenous route and subsequently measuring the initial plasma concentration of the drug. The formula is as follows:

**$V_d$ (L) = amount of drug given (mg) / plasma concentration of drug (mg/L)**

The average total body water is approximately 41 liters. Of that, the extracellular fluid volume is about 14 L, or 1/3 of total body water. Within the extracellular fluid, the plasma volume is about 3 L, and interstitial fluid makes up the rest. Initially, the drug enters the plasma compartment by the IV route. If a drug has a large molecular weight, is bound extensively to plasma proteins, or is highly charged (hydrophilic), then the drug generally remains in the plasma compartment and the volume of distribution is usually low as in the case above (about 3-5 liters). If the drug has a small molecular weight but is hydrophilic, it can distribute into the interstitial fluid compartment outside of the blood vessels as well as in the intravascular compartment. In these cases the volume of distribution is limited to a total volume of about 14-16 liters (plasma volume plus interstitial volume). If the drug has a small molecular weight and is also uncharged (hydrophobic or lipophilic), then the drug can cross cell membranes and reach intracellular compartment. These drugs have the highest volume of distribution (41 liters). Drugs that are avidly bound in the tissues exhibit the highest volumes of distribution, often much higher than the total body water volume, because these drugs accumulate readily within cells thereby maintaining low plasma concentrations.

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A new aminoglycoside antibiotic is developed that is believed to be particularly effective against *Pseudomonas*. The volume of distribution of the drug is measured in a group of volunteers and is determined to be 4.5 L. This new drug is most likely to have which of the following properties?

- A. It has low molecular weight (4%)
- B. It is lipophilic (28%)
- ✗ C. It does not bind to albumin (13%)
- ✓ D. It is highly charged (39%)
- E. It has high oral bioavailability (13%)

Incorrect
Correct answer
D

39%
Answered correctly

03 secs
Time Spent

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## Explanation

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Submit

lipophilicity and a high volume of distribution. Highly lipophilic drugs tend to be poorly eliminated in the kidney as these agents rapidly cross tubular cell membranes after filtration to reenter the tissues.

High lipophilicity (lipid solubility) allows the drug to cross cellular barriers more easily and enter hepatocytes. It can then be excreted in the bile or through other methods of elimination. In addition, high lipid solubility assures a wide distribution to many different tissues including the brain, liver, and adipose tissue.

**(Choice A)** Drugs with a low distribution volume tend to be confined to the bloodstream and tend not to diffuse readily through hepatocytes into the bile. Thus, a drug with a low $V_d$ will be highly plasma protein-bound and hydrophilic, making it less available for hepatic metabolism and more readily available for excretion unchanged in the urine.

**(Choice B)** A drug that is not well absorbed orally may have a high pre-systemic (first-pass) elimination or be poorly lipid-soluble. In both cases, it will be unavailable to the liver for hepatic clearance.

**(Choice D)** A low rate of redistribution from one compartment to another implies low lipid solubility or significant hydrophilicity. These drugs tend to remain in the intravascular compartment and be eliminated by the kidneys.

**(Choice E)** Poor central nervous system penetration indicates that a drug is likely not lipophilic, and therefore has a low volume of distribution. It is therefore also unlikely that the same drug will be eliminated in large amounts by the liver.

**Educational Objective:**
While the kidney is the primary site of elimination of most drugs, the liver is the main site of biotransformation of these agents in preparation for elimination. Drugs that are more lipophilic (high $V_d$, good penetration into CNS) are preferentially processed by the liver into more polar compounds for easier elimination in the bile and urine. Liver disease (e.g., cirrhosis) or the concomitant use of other drugs may limit or enhance the clearance of drugs metabolized in the liver.

Pharmacology  Pharmacology (General Principles)  Drug structure and properties

The kidney is the primary site of excretion of most drugs, with or without prior chemical modification in the liver. The liver is the major site of drug biotransformation and metabolism, but some drugs are also predominately eliminated by the liver into the bile and feces. Drugs with high intrinsic hepatic clearance tend to have high lipophilicity and a high volume of distribution. Highly lipophilic drugs tend to be poorly eliminated in the kidney as these agents rapidly cross tubular cell membranes after filtration to reenter the tissues.

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A 57-year-old man with severe pyelonephritis is admitted to the hospital. His past medical history is significant for diabetes, hypertension, and two episodes of transient ischemic attacks. His serum creatinine level is 3.2 mg/dL; therefore, he needs to be started on an antibiotic that depends mainly on non-renal clearance. Which of the following characteristics should the antibiotic also have if hepatic metabolism and clearance is desired?

- ✗ A. Low volume of distribution (17%)
- B. Poor oral absorption (8%)
- ✓ C. High lipophilicity (57%)
- D. Low rate of redistribution (12%)
- E. Poor penetration into the CNS (4%)

Incorrect
Correct answer
C

57%
Answered correctly

04 secs
Time Spent

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## Explanation

The kidney is the primary site of excretion of most drugs, with or without prior chemical modification in the liver. The liver is the major site of drug biotransformation and metabolism, but some drugs are also predominately eliminated by the liver into the bile and feces. Drugs with high intrinsic hepatic clearance tend to have high lipophilicity and a high volume of distribution. Highly lipophilic drugs tend to be poorly eliminated in the kidney as these agents rapidly cross tubular cell membranes after filtration to reenter the tissues.

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Submit

| | | |
|---|---|---|
| **Serotonin (5-$HT_3$) receptor antagonists** | • Ondansetron<br>• Granisetron | • Chemotherapy-induced emesis |
| **Neurokinin 1 (NK1) receptor antagonists** | • Aprepitant<br>• Fosaprepitant | |

Perception of motion and orientation is determined by input from the vestibular, visual, and somatosensory systems. These 3 systems are usually congruent, but conflicting input can lead to **motion sickness**, characterized by nausea, dizziness, and autonomic symptoms (eg, diaphoresis). Integration of these sensory pathways occurs in the **vestibular nuclei** via muscarinic and histaminic neurotransmission. As such, **antimuscarinic** agents (eg, scopolamine) and first-generation **antihistamines** (eg, meclizine, dimenhydrinate) are most effective for management of motion sickness. **Anticholinergic side effects** are common with these medications and may include blurry vision, dry mouth, urinary retention, and constipation.

**(Choices A, D, and E)** Cough, frequent urination, and nasal congestion are characteristic of stimulation rather than blockade of muscarinic pathways.

**(Choice B)** Diarrhea may be seen with dopamine receptor antagonists (eg, metoclopramide), but these drugs are primarily used for visceral (eg, diabetic gastroparesis), rather than vestibular, nausea.

**Educational objective:**
Antimuscarinic agents and antihistamines with antimuscarinic action are most effective for motion sickness prevention.

**References**

- Scopolamine (hyoscine) for preventing and treating motion sickness.

Pharmacology — Subject
Pharmacology (General Principles) — System
Motion sickness — Topic

Explanation

| Characteristics of antiemetic drugs | | |
|---|---|---|
| **Drug class** | **Examples** | **Clinical uses** |
| **Antimuscarinics (anticholinergics)** | • Scopolamine | • Motion sickness<br>• Hyperemesis gravidarum (promethazine) |
| **Antihistamines** | • Diphenhydramine<br>• Meclizine<br>• Promethazine | |
| **Dopamine receptor antagonists** | • Prochlorperazine<br>• Metoclopramide | • Chemotherapy-induced emesis |
| **Serotonin (5-$HT_3$) receptor antagonists** | • Ondansetron<br>• Granisetron | |
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A 38-year-old woman comes to the office to discuss motion sickness. She is currently feeling well. The patient is planning a vacation cruise and has previously experienced severe nausea and vomiting while sailing. She has 4 children, and her past medical history is notable only for a tubal ligation. The patient does not smoke and drinks only moderate quantities of alcohol. She is not currently taking any medications. Physical examination, including otologic and neurologic examinations, is normal. After the appropriate drug therapy is recommended, this patient should be counseled regarding which of the following side effects?

- A. Cough (1%)
- ✗ B. Diarrhea (6%)
- ✓ C. Dry mouth (87%)
- D. Frequent urination (2%)
- E. Nasal congestion (1%)

Incorrect
Correct answer
C

87%
Answered correctly

03 secs
Time Spent

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Version

Explanation

| Characteristics of antiemetic drugs | | |
|---|---|---|
| **Drug class** | **Examples** | **Clinical uses** |
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| | • Diphenhydramine | |

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- B. Diarrhea
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Submit

population: one that rapidly converts the drug into its metabolite (considered normals) and another that converts the drug slowly, leading to accumulation of the original drug in the plasma.

Isoniazid is metabolized by acetylation to N-acetyl-isoniazid in the hepatic microsomal system by the enzyme N-acetyl transferase and is subsequently excreted in the urine. The first and second peaks in the above graph represent fast and slow acetylators, respectively. Slow acetylators of isoniazid also metabolize (acetylate) dapsone, hydralazine, and procainamide slowly, causing accumulation of these drugs as well. Slow acetylators of these drugs are at increased risk of toxic effects, while fast acetylators may require much higher therapeutic doses to achieve a therapeutic effect.

**(Choice A)** Methylation is an important drug biotransformation method to consider when prescribing drugs such as azathioprine and 6-mercaptopurine, drugs used in the treatment of some inflammatory disorders of the bowel and skin.

**(Choice B)** Glucuronidation is a biotransformation pathway utilized for the metabolism of numerous drugs as well as endogenous substances such as bilirubin. No bimodality has been described with this pathway, but conditions such as Gilbert syndrome involve dysfunction of the glucuronyl transferase system that can lead to toxic accumulation of some drugs.

**(Choice C)** Hydrolysis occurs with enzymes such as esterases and amidases. Isoniazid is not metabolized by this pathway, and hydrolysis does not exhibit polymorphic metabolism.

**(Choice E)** Amine oxidation is usually undertaken by monoamine oxidases or by cytochrome oxidative deamination. Neither process metabolizes isoniazid nor exhibits bimodality.

**Educational Objective:**
Isoniazid is metabolized by acetylation. The speed with which a patient is able to acetylate drugs depends on whether they are genetically "fast" or "slow" acetylators. The presence of fast and slow acetylators within the same population results in a bimodal distribution of the speed of isoniazid metabolism. Slow acetylators are at increased risk of adverse side effects.

Explanation

The rate and extent of drug metabolism normally varies from person to person. These slight interpersonal variations in the ability to metabolize drugs are typically reflected graphically by a unimodal distribution, usually in the shape of a bell curve, when plasma levels of drug are measured at a fixed time following a fixed dose of drug. This is the method that was used to generate the graph given in the question stem. With most drugs, the majority of people fall within one standard deviation and 95% of people fall within two standard deviations of the population mean of plasma concentration. A single peak in this type of graph indicates that the population being tested possesses a similar genetic drug metabolizing capacity.

A bimodal (discontinuous, polymorphic) curve, as shown in the question stem, results from the presence of two apparently distinct groups within the study population and suggests a pharmacogenetic polymorphism in drug metabolizing capacity. In other words, the two peaks indicate two sets of responders to the drug within the population: one that rapidly converts the drug into its metabolite (considered normals) and another that converts the drug slowly, leading to accumulation of the original drug in the plasma.

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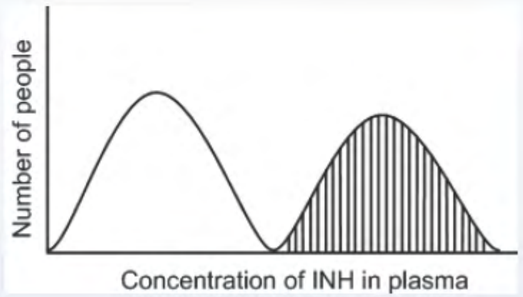
A group of investigators is performing an experiment designed to assess genetic variability in drug biotransformation. A fixed dose of isoniazid is given to a group of volunteers, and the plasma drug concentration is measured four hours following administration of the drug. The following distribution of plasma drug concentration in these subjects is obtained.




Variation of which of the following processes provides the best explanation for the shaded area of the curve?

- A. Methylation (7%)
- ✗ B. Glucuronidation (19%)
- C. Hydrolysis (8%)
- ✓ D. Acetylation (59%)
- E. Amine oxidation (5%)

Incorrect
Correct answer
D

59%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

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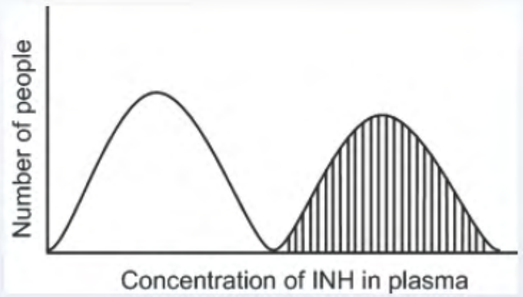


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- C. Hydrolysis
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- E. Amine oxidation

Submit

| findings | • ± Elevated bilirubin & alkaline phosphatase |
|---|---|

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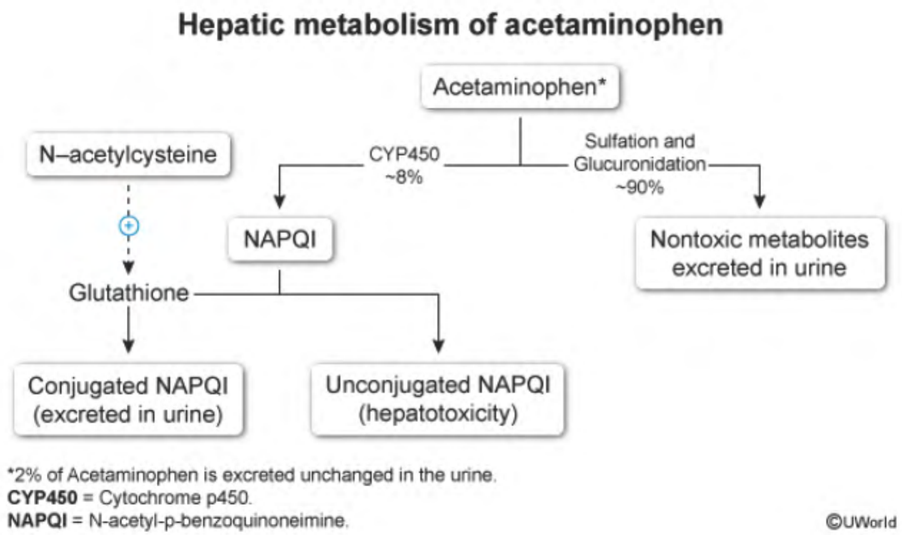


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bilirubin), and aminotransferase levels are typically normal.

doses, glutathione becomes saturated, allowing excessive amounts of NAPQI to form adducts with hepatic proteins that **disrupt hepatocyte mitochondrial function** and cause **oxidative injury**.

Because acetaminophen-induced liver injury primarily affects hepatocytes (ie, **hepatocellular liver injury**), laboratory findings show markedly **elevated aminotransferases** with levels sometimes >1,000 U/L. Mild elevations of bilirubin and alkaline phosphatase can be seen but may be normal. Liver biopsy shows centrilobular hepatic necrosis, a common finding in ischemic or toxic liver injury.

**(Choice A)** Certain drugs (eg, carbamazepine, phenytoin) can trigger a robust $CD4^+$ and $CD8^+$ T-cell response against hepatic proteins, leading to drug reaction with eosinophilia and systemic symptoms (DRESS). Although hepatocellular liver injury can occur, fever, lymphadenopathy, and skin manifestations (eg, facial edema, coalescing erythema) would be expected.

**(Choice B)** Drug-mediated (eg, ceftriaxone) cholestatic liver injury typically causes biliary duct damage or interrupts the flow of bile. These patients have markedly elevated levels of alkaline phosphatase (and sometimes bilirubin), and aminotransferase levels are typically normal.

**(Choice D)** Microvesicular steatohepatitis, or small droplets of intracytoplasmic lipids within hepatocytes, is caused by drugs that disrupt fatty acid beta-oxidation. Ibuprofen and aspirin are commonly used analgesics that can rarely lead to this condition; however, marked aminotransferase elevations are not seen in ibuprofen toxicity, and aspirin toxicity is usually seen in young children with a recent viral infection (ie, Reye syndrome).

**(Choice E)** Chronic alcohol consumption can generate reactive oxygen species (ROS), which activate stellate cells and cause cirrhosis. Although NAPQI does create ROS, stellate cell activation does not occur, and this patient's acute liver injury after analgesic ingestion makes this diagnosis unlikely.

**Educational objective:**
Excessive acetaminophen use causes toxicity through its metabolite N-acetyl-p-benzoquinone imine, which disrupts hepatocyte mitochondrial function and induces oxidative injury throughout the liver. The resulting hepatocellular liver injury markedly elevates aminotransferase, with levels sometimes exceeding 1,000 U/L.

This patient who took large quantities of a pain medication initially had nausea and vomiting and has now developed scleral icterus, right upper quadrant pain, and markedly elevated aminotransferases. These findings are consistent with an overdose of **acetaminophen**, a commonly used analgesic.

When taken at appropriate doses, acetaminophen produces small amounts of the **toxic metabolite** N-acetyl-p-benzoquinone imine (NAPQI), which is conjugated with glutathione in the liver and excreted. At supratherapeutic doses, glutathione becomes saturated, allowing excessive amounts of NAPQI to form adducts with hepatic proteins that **disrupt hepatocyte mitochondrial function** and cause **oxidative injury**.

Because acetaminophen-induced liver injury primarily affects hepatocytes (ie, **hepatocellular liver injury**), laboratory findings show markedly **elevated aminotransferases** with levels sometimes >1,000 U/L. Mild elevations of bilirubin and alkaline phosphatase can be seen but may be normal. Liver biopsy shows centrilobular hepatic necrosis, a common finding in ischemic or toxic liver injury.

**(Choice A)** Certain drugs (eg, carbamazepine, phenytoin) can trigger a robust $CD4^+$ and $CD8^+$ T-cell response against hepatic proteins, leading to drug reaction with eosinophilia and systemic symptoms (DRESS). Although hepatocellular liver injury can occur, fever, lymphadenopathy, and skin manifestations (eg, facial edema, coalescing erythema) would be expected.

**(Choice B)** Drug-mediated (eg, ceftriaxone) cholestatic liver injury typically causes biliary duct damage or interrupts the flow of bile. These patients have markedly elevated levels of alkaline phosphatase (and sometimes bilirubin), and aminotransferase levels are typically normal.

**(Choice D)** Microvesicular steatohepatitis, or small droplets of intracytoplasmic lipids within hepatocytes, is caused by drugs that disrupt fatty acid beta-oxidation. Ibuprofen and aspirin are commonly used analgesics that can rarely lead to this condition; however, marked aminotransferase elevations are not seen in ibuprofen toxicity, and aspirin toxicity is usually seen in young children with a recent viral infection (ie, Reye syndrome).

**(Choice E)** Chronic alcohol consumption can generate reactive oxygen species (ROS), which activate stellate

| Acetaminophen overdose | |
|---|---|
| **Pathophysiology** | • Depletion of intrahepatic glutathione → overaccumulation of NAPQI<br>• NAPQI forms adduct with mitochondrial proteins → oxidative hepatocellular injury |
| **Clinical features** | • Initially asymptomatic or nonspecific (eg, nausea, vomiting, malaise)<br>• Can progress to right upper quadrant pain, jaundice, hepatic encephalopathy & bleeding diathesis |
| **Laboratory findings** | • Normal until 24 hr after ingestion<br>• ↑↑ AST, ALT (often >1,000 U/L)<br>• ↑ PT, PTT when severe<br>• ± Elevated bilirubin & alkaline phosphatase<br>• Liver biopsy: centrilobular necrosis |
| **Treatment** | • N-acetylcysteine: repletes intrahepatic glutathione stores |
| **ALT** = alanine aminotransferase; **AST =** aspartate aminotransferase; **NAPQI** = N-acetyl-p-benzoquinone imine. | |

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A 16-year-old girl is brought to the emergency department because of progressively increasing nausea, vomiting and right upper quadrant pain. She was initially seen in the emergency department 24 hours ago for nausea and vomiting but was discharged when her examination and laboratory studies were unremarkable. At today's visit, the patient reveals, "I am so upset. My boyfriend broke up with me and I have been taking a lot of pain medication to relieve my pain." Temperature is 37.1 C (98.8 F), blood pressure is 108/70 mm Hg, pulse is 102/min, and respirations are 16/min. Pulse oximetry is 98% on room air. On examination, scleral icterus and marked right upper quadrant tenderness are present. Pupils are normal in size and reactive to light. Neurologic examination shows no abnormalities. Laboratory results are as follows:

| | |
|---|---|
| Total bilirubin | 1.3 mg/dL |
| Alkaline phosphatase | 120 U/L |
| Aspartate aminotransferase (SGOT) | 3,906 U/L |
| Alanine aminotransferase (SGPT) | 4,014 U/L |

Which of the following is the most likely underlying mechanism of drug toxicity in this patient?

- A. Cytotoxic T-cell response to hepatocyte proteins (2%)
- ✗ B. Drug-mediated inhibition of bile flow (2%)
- ✓ C. Drug metabolite–induced mitochondrial dysfunction (67%)
- D. Drug–induced disruption of fatty acid metabolism (5%)
- E. Reactive oxygen species–induced stellate cell activation (22%)

Incorrect
Correct answer
C

67%
Answered correctly

03 secs
Time Spent

2023
Version

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Submit

increased toxicity. **Decreased cardiac output** leads to tissue hypoperfusion, lowering the volume of distribution of many drugs and **reducing perfusion** of organs responsible for **drug clearance** (eg, liver, kidneys). This can result in higher serum drug levels and a prolonged elimination phase, which can be particularly important for drugs with a narrow therapeutic index (eg, digoxin, antiarrhythmics).

In this example, **serum metformin levels** are seen to **increase** in animals with experimentally induced heart failure. Because metformin is **renally cleared**, this effect is most likely due to **decreased renal blood flow** as a result of reduced cardiac output. Because of the risk of lactic acidosis, metformin should be used with caution in patients with heart failure or impaired renal function from other causes.

**(Choices A and D)** Heart failure frequently causes high central venous pressure and hepatic congestion. The resulting impairment in nutrient and oxygen delivery leads to hepatocellular damage and downregulation of CYP enzymes involved in drug metabolism. Reduced hepatic blood flow also results in decreased drug delivery to the liver, further impairing hepatic drug metabolism and clearance. However, metformin is not metabolized by the liver; it is excreted unchanged by the kidney.

**(Choice C)** Decreased tissue perfusion in heart failure typically leads to a reduced volume of distribution of most drugs. Although the *extracellular fluid accumulation* that occurs in decompensated heart failure can potentially increase the volume of distribution of water-soluble drugs, this increased distribution volume would result in a *decrease* in serum drug levels.

**(Choice E)** Increased central venous pressure in heart failure can lead to intestinal wall edema with increased intestinal wall thickness. This can result in delayed or decreased intestinal drug absorption. However, this effect would be expected to cause reduced serum drug concentrations and delayed peak levels.

**Educational objective:**
Heart failure leads to reduced liver and kidney perfusion, resulting in reduced drug clearance. Metformin is excreted unchanged by the kidney; therefore, patients with significant renal insufficiency due to heart failure or other causes (eg, chronic kidney disease) are at increased risk of toxicity (eg, lactic acidosis).

**Heart failure** can cause changes in pharmacokinetic parameters that can alter drug effectiveness and lead to increased toxicity. **Decreased cardiac output** leads to tissue hypoperfusion, lowering the volume of distribution of many drugs and **reducing perfusion** of organs responsible for **drug clearance** (eg, liver, kidneys). This can result in higher serum drug levels and a prolonged elimination phase, which can be particularly important for drugs with a narrow therapeutic index (eg, digoxin, antiarrhythmics).

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Explanation

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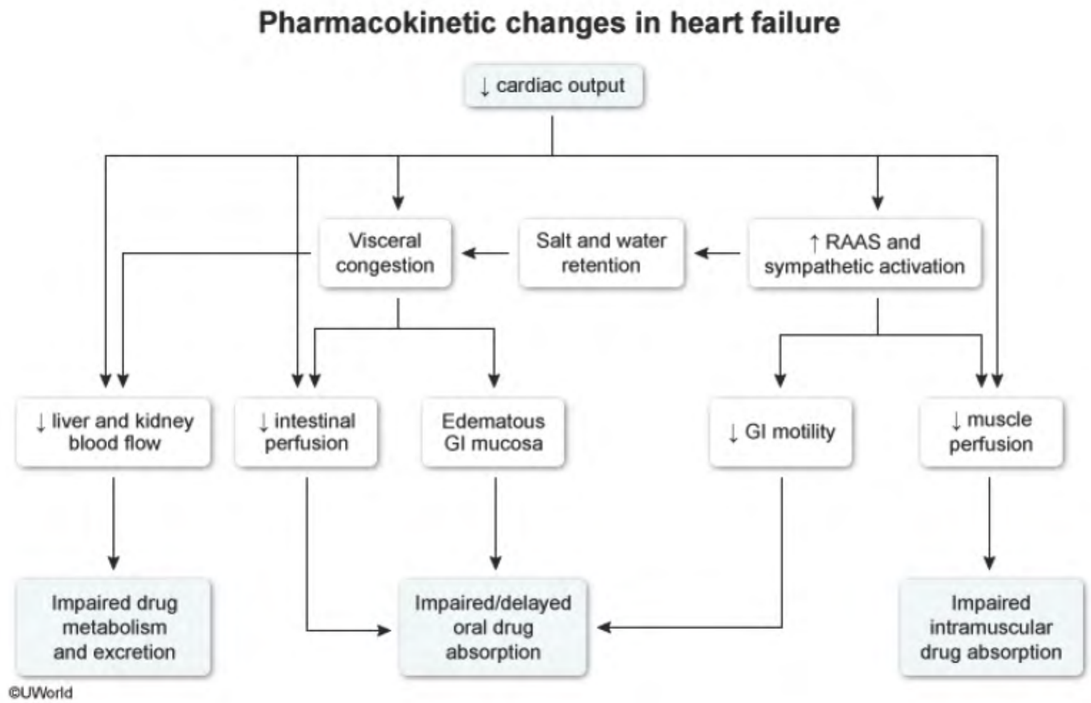


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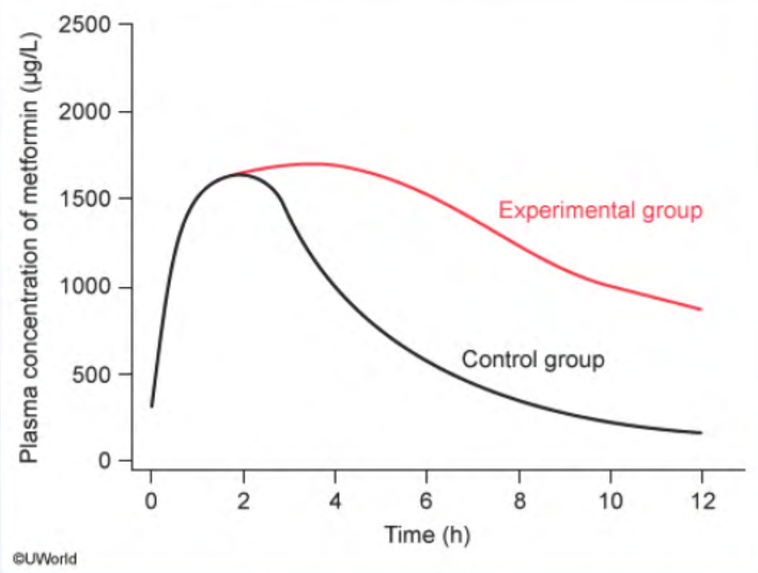
administered an oral dose of metformin, and serum levels are monitored over time. The test is repeated in control animals with normal heart function and the results are shown below:




Which of the following best explains the change in serum metformin levels seen in the experimental animals?

- A. Cytochrome P450 inhibition (6%)
- ✓ B. Decreased renal blood flow (78%)
- C. Extracellular fluid accumulation (5%)
- D. Hepatic venous congestion (8%)
- ✗ E. Intestinal wall edema (0%)

Incorrect
Correct answer
B

78%
Answered correctly

04 secs
Time Spent

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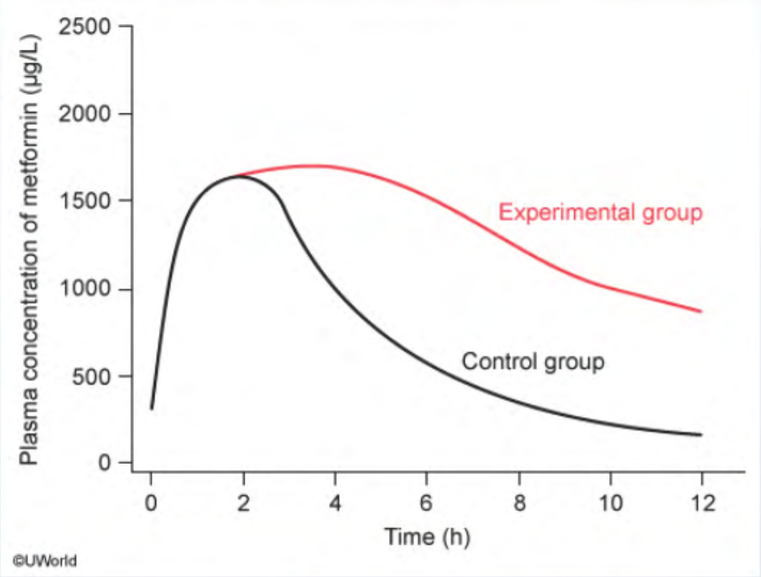
Researchers investigating the effects of heart failure on the pharmacokinetics of antidiabetic medications develop a cohort of experimental animals with anthracycline-induced heart failure. The experimental animals are then administered an oral dose of metformin, and serum levels are monitored over time. The test is repeated in control animals with normal heart function and the results are shown below:

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- B. Decreased renal blood flow
- C. Extracellular fluid accumulation
- D. Hepatic venous congestion
- E. Intestinal wall edema

- **Drug clearance (CL)**, or volume of plasma cleared of drug per unit time (eg, mL/min)

Multiplying these two parameters gives the elimination rate, or the amount of drug eliminated from the body per unit of time:

$$\text{Elimination rate} = C_{ss} \times CL$$

The maintenance dose can then be calculated for the appropriate dosing interval (eg, 12 hr) by multiplying the elimination rate ($C_{ss} \times CL$) by the **time between doses**:

$$\textbf{Maintenance dose} = \mathbf{C_{ss} \times CL \times \text{dosing interval}}$$

**(Choice B)** When a drug is administered more quickly than it can be eliminated from the body, it accumulates until a steady-state level is reached; as plasma concentration increases, the amount of drug eliminated also increases until the amount administered equals the amount eliminated. When a drug is administered at regular intervals, the time needed to reach the steady state level depends only on the drug half-life (ie, it takes 5 half-lives to reach 97% of the steady-state level); the exact size of each dose or interval between doses does not matter.

**(Choices C, D, and E)** Loading doses are larger than maintenance doses and can be used during treatment initiation to shorten the time needed to reach target steady-state plasma concentrations. They are most useful when an immediate therapeutic response is needed (eg, life-saving antibiotics) or when using drugs with large volumes of distribution (eg, amiodarone). Total body weight influences the volume of distribution and is often used when calculating the loading dose. However, these parameters are not needed when calculating the maintenance dose because the amount of drug lost per unit of time depends only on the steady-state plasma concentration and drug clearance.

**Educational objective:**
Clearance (CL) determines the dose rate required to maintain a given steady-state plasma concentration ($C_{ss}$):

$$\text{Maintenance dose} = C_{ss} \times CL \times \text{dosing interval}$$

Most drugs are administered in the form of repetitive, intermittent doses designed to achieve a steady-state plasma concentration within a targeted therapeutic range. The amount of each dose is calculated so that the administered dose is just enough to replace the amount of drug eliminated by the body since the last dose. This replacement dose **(maintenance dose)** depends on both of the following:

- **Steady-state plasma concentration ($C_{ss}$)**
- **Drug clearance (CL)**, or volume of plasma cleared of drug per unit time (eg, mL/min)

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Explanation

| Pharmacokinetic parameter | Formula | Note |
|---|---|---|
| **Half life** | $V_d \times 0.7 / CL$ | Steady-state concentration is achieved in 4-5 half-lives. |
| **Maintenance dose** | $C_{ss} \times CL \times$ dosing interval | Maintenance dose is decreased in patients with renal or hepatic impairment. |
| **Loading dose** | $V_d \times C_{ss}$ | Loading dose is affected by body weight and composition. |
| **CL** = drug clearance; **Css** = steady-state plasma concentration; **Vd** = volume of distribution. | | |

Most drugs are administered in the form of repetitive, intermittent doses designed to achieve a steady-state plasma concentration within a targeted therapeutic range. The amount of each dose is calculated so that the administered dose is just enough to replace the amount of drug eliminated by the body since the last dose. This replacement dose **(maintenance dose)** depends on both of the following:

- **Steady-state plasma concentration ($C_{ss}$)**
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Multiplying these two parameters gives the elimination rate, or the amount of drug eliminated from the body per unit of time:

$$\text{Elimination rate} = C_{ss} \times CL$$

A 37-year-old man comes to the emergency department due to fever, chills, and malaise. He has no significant medical history but he uses illicit intravenous drugs on a regular basis. The patient is febrile, tachycardic, and hypotensive. Auscultation reveals a heart murmur. A preliminary diagnosis of infective endocarditis is established. Blood cultures grow methicillin-resistant *Staphylococcus aureus*, and the patient is prescribed an intravenous antibiotic administered every 12 hours. Calculation of the maintenance dose will most likely require which of the following parameters?

- ✓ A. Drug clearance rate (63%)
- ✗ B. Number of doses needed to reach steady state (6%)
- C. Size of the loading dose (3%)
- D. Total body weight of the patient (8%)
- E. Volume of distribution of the drug (18%)

Incorrect
Correct answer
A

63%
Answered correctly

04 secs
Time Spent

2023
Version

Explanation

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|---|---|---|
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- E. Volume of distribution of the drug

Submit

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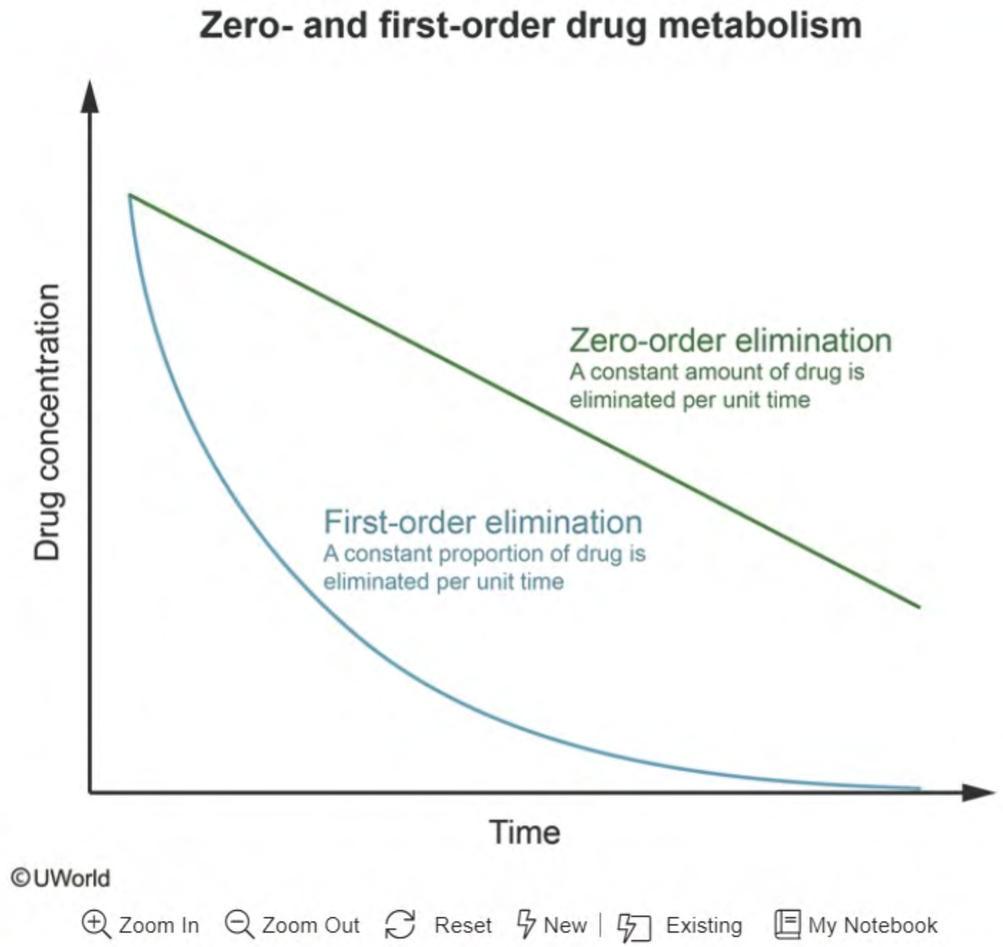


Pharmacology Pharmacology (General Principles) Drug metabolism and clearance

rise with increasing doses of the substrate drug. At this point (2 on the graph), the kinetics change from first- to **zero-order kinetics** and the graph levels out to a zero slope. With zero-order kinetics, **a constant amount** of drug is metabolized and eliminated per unit of time regardless of its concentration or dose.

Zero- and first-order kinetics can also be represented graphically by showing the decrease in drug concentration over time after a single dose. Zero-order metabolism is indicated by a straight line with negative slope (fixed amount eliminated per unit of time), whereas first-order kinetics manifest as an exponential decay curve (fixed proportion eliminated per unit of time).

**(Choice A)** After point 3, the curve remains flat, indicating that a constant amount of drug is metabolized per unit of time regardless of the dose. As higher doses are administered, the proportion that is converted to the metabolite becomes smaller (ie, the proportion metabolized is non-constant after point 3).

**(Choice B)** Bioavailability is the fraction of an administered drug that reaches the systemic circulation unchanged. It usually decreases with oral administration due to incomplete absorption and first-pass metabolism compared to parenteral administration. In this case, higher doses of the drug are likely to have greater bioavailability due to the saturation of hepatic metabolism.

**(Choice C)** At point 2, biotransformation (ie, metabolism) of the drug begins to switch from first-order to zero-order kinetics due to enzyme saturation. However, drug metabolism does not stop.

**(Choice E)** Before point 1, drug metabolism proceeds via first-order kinetics. Therefore, the drug metabolization rate increases as higher doses are administered.

**Educational objective:**
In first-order kinetics, a constant fraction (or proportion) of drug is metabolized per unit of time, so the amount metabolized changes based on the serum concentration. In zero-order kinetics, a constant amount of drug is metabolized per unit of time, independent of serum levels.

Pharmacology  Pharmacology (General Principles)  Drug metabolism and clearance

The drug under investigation is glucuronated by the liver into water-soluble byproducts that can then be excreted by the kidney. The graph above shows how the **rate of drug glucuronidation** changes with increasing drug doses. At lower doses, the quantity of drug-glucuronide formed is directly proportional to the dose administered (ie, as more of the drug is administered, more drug-glucuronide is produced). Because a **fixed proportion** of drug is converted to the metabolite, this early portion of the graph represents **first-order kinetics**.

As the active sites on glucuronosyltransferase become saturated, the drug-glucuronide rate does not continue to rise with increasing doses of the substrate drug. At this point (2 on the graph), the kinetics change from first- to **zero-order kinetics** and the graph levels out to a zero slope. With zero-order kinetics, **a constant amount** of drug is metabolized and eliminated per unit of time regardless of its concentration or dose.

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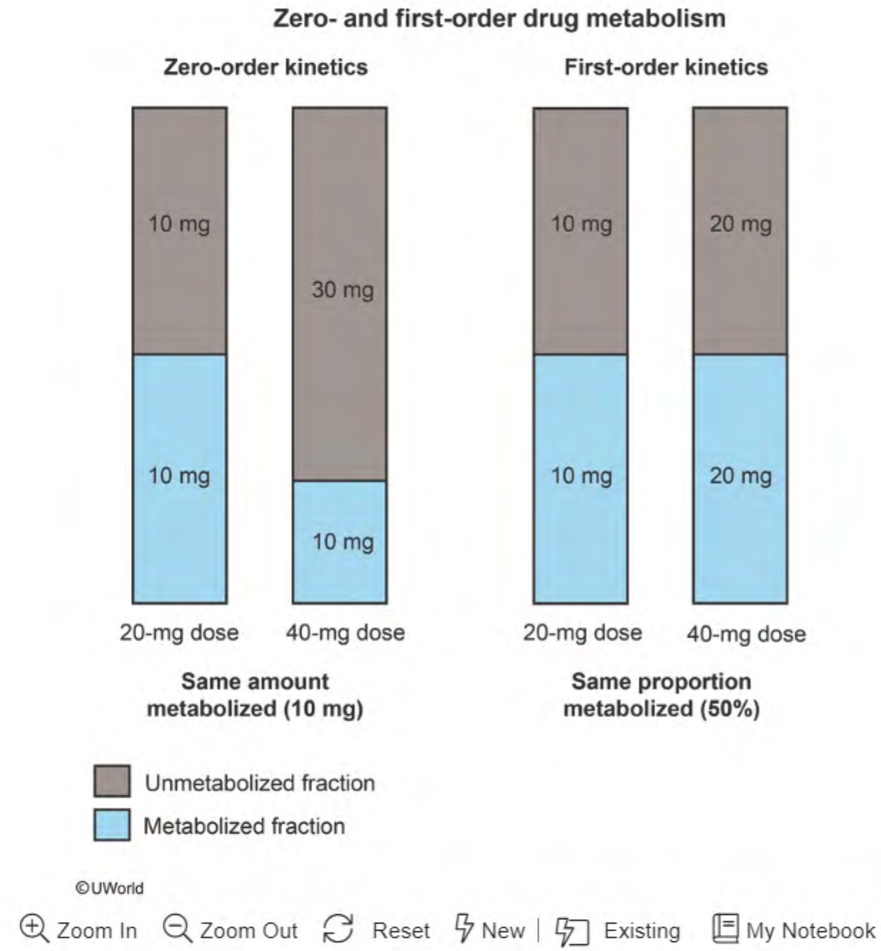


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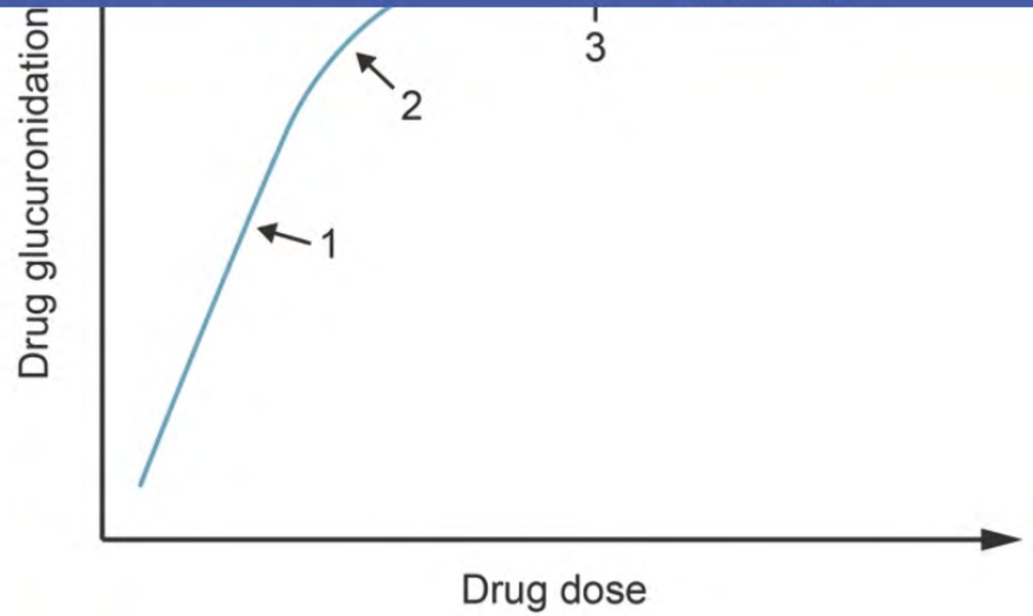
Same amount metabolized (10 mg)
Same proportion metabolized (50%)






Which of the following is the most accurate statement about this drug's metabolism?

- A. A constant proportion of the drug is metabolized past point 3 (37%)
- ✗ B. Bioavailability of the drug is highest at point 1 (5%)
- C. Biotransformation of the drug ceases near point 2 (5%)
- ✓ D. Metabolism begins to switch to zero-order kinetics near point 2 (47%)
- E. The rate of drug metabolism is not dependent on dose before point 1 (3%)

Incorrect
Correct answer
D

47%
Answered correctly

09 secs
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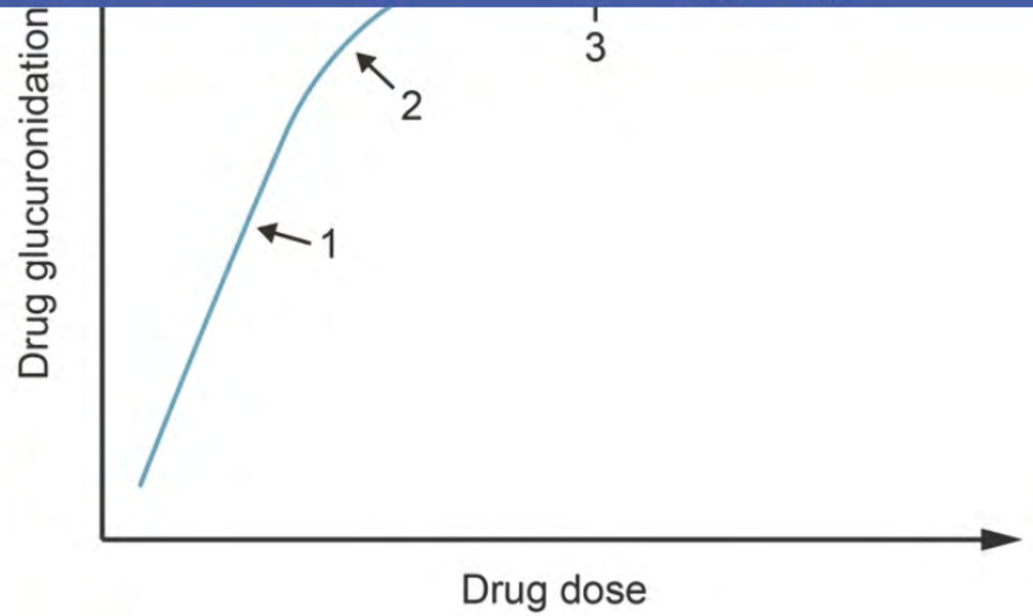




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- C. Biotransformation of the drug ceases near point 2
- D. Metabolism begins to switch to zero-order kinetics near point 2
- E. The rate of drug metabolism is not dependent on dose before point 1

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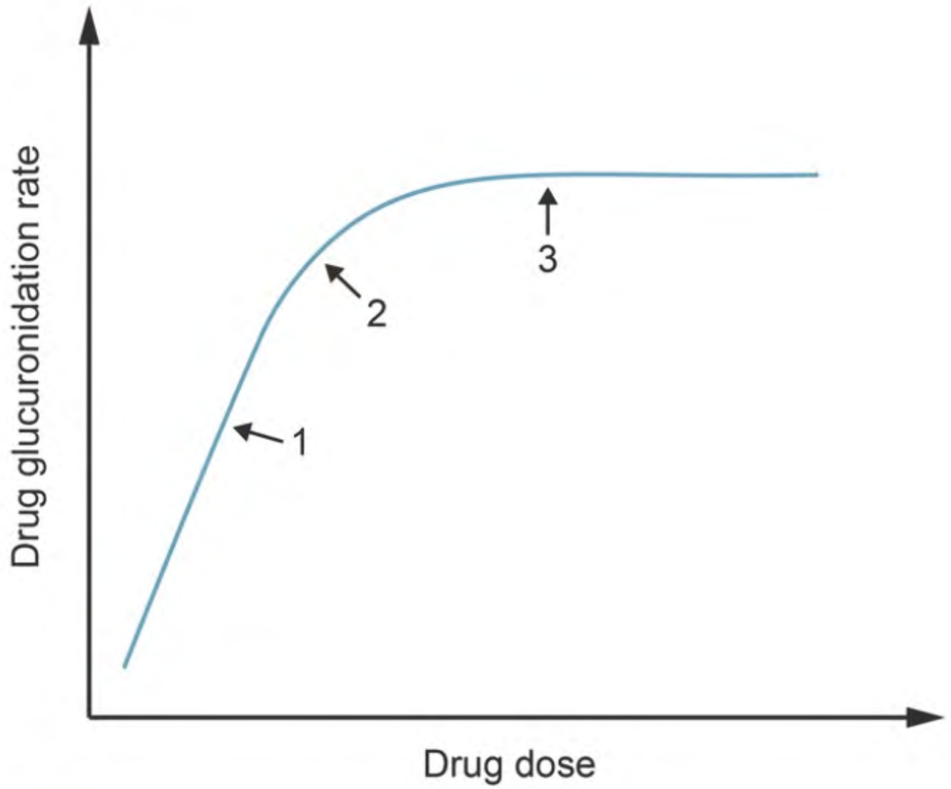




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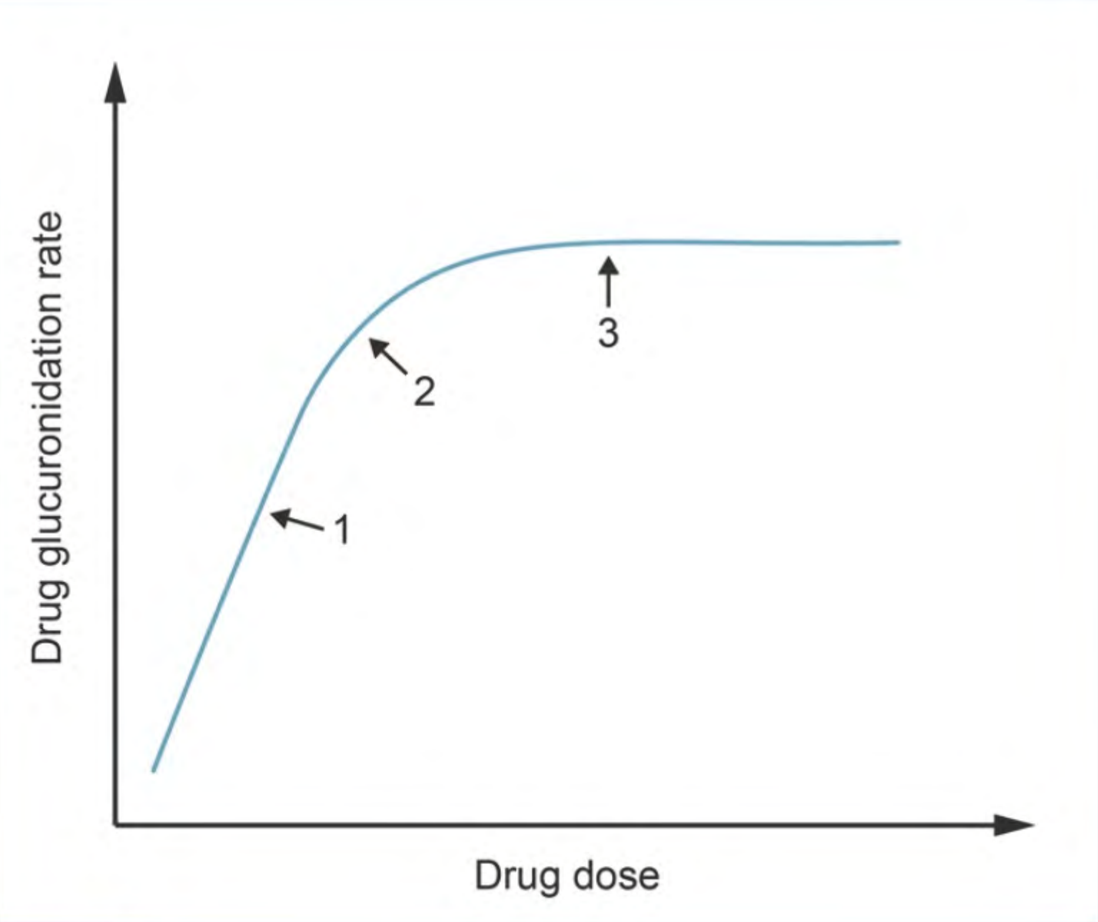
Drug dose

A large, multinational drug corporation conducts a phase I clinical trial to evaluate the safety profile and pharmacokinetic properties of a new drug designed to treat refractory epilepsy. Initial studies in animals showed that the drug undergoes extensive metabolism by the liver into glucuronidation byproducts that are primarily excreted by the kidneys. The curve below demonstrates the glucuronidation rate of the drug over a wide range of doses.



**Monoclonal antibodies** (mAbs) are used to treat a growing variety of malignant (eg, leukemia/lymphoma, melanoma) and autoimmune diseases (eg, Crohn disease, rheumatoid arthritis). The therapeutic effect of mAbs is achieved by binding to their target antigen in the plasma or on the cell surface and **blocking deleterious receptor interactions** or triggering a **cytotoxic immune response** against abnormal cells.

Because of their large molecular size, mAbs cannot be administered orally and must be given via intravenous or subcutaneous/intramuscular routes. Unlike most other drugs, mAbs are **not eliminated by hepatic or renal clearance**, but are instead removed from the body in 2 primary ways:

- Target-mediated drug clearance: mAbs directed against cell surface antigens undergo internalization (receptor-mediated endocytosis) upon binding to their targets, removing them from the circulation
- Nonspecific clearance: Immunoglobulins are constitutively taken up by reticuloendothelial macrophages (via binding to Fc receptors) and vascular endothelial cells (via pinocytosis)

Once internalized, immunoglobulins are **catabolized into amino acids** within lysosomes.

**(Choices A and C)** Many drugs undergo modifications by the cytochrome P450 system and subsequent conjugation reactions within hepatocytes that help facilitate excretion of the drug into the urine or bile. In contrast, immunoglobulins are not metabolized by these systems, but rather broken down by proteolytic enzymes.

**(Choices B and D)** Immunoglobulins are too large to undergo substantial filtration at the glomerular basement membrane and are not secreted by the renal tubules. Therefore, renal dysfunction does not significantly affect monoclonal antibody clearance.

**Educational objective:**
Monoclonal antibodies (mAbs) are not eliminated by hepatic or renal clearance. Therefore, no dose adjustment is necessary with impaired hepatic/renal function or use of cytochrome P450 inducers or inhibitors.

**References**

A clinical trial is being conducted to evaluate the safety and efficacy of a novel therapy to treat refractory Crohn disease. The medication is a monoclonal antibody against the α4β7 integrin, which inhibits migration of T-lymphocytes into the intestinal parenchyma and produces a gut-selective anti-inflammatory effect. Patients who have active, moderate to severe Crohn disease and have failed conventional therapy are enrolled in the study. Many of these patients have renal or hepatic dysfunction, and some take other medications that affect cytochrome P450 enzymes. Which of the following is the most appropriate dose adjustment in this patient population to decrease drug toxicity?

- A. Higher dose in patients taking cytochrome P450 inducers (17%)
- ✗ B. Lower dose in patients with decreased glomerular filtration (21%)
- C. Lower dose in patients with hepatocellular dysfunction (21%)
- D. Lower dose in patients with renal tubular dysfunction (7%)
- ✓ E. No dose adjustment necessary (32%)

Incorrect
Correct answer
E

32%
Answered correctly

05 secs
Time Spent

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Version

Explanation

**Monoclonal antibodies** (mAbs) are used to treat a growing variety of malignant (eg, leukemia/lymphoma, melanoma) and autoimmune diseases (eg, Crohn disease, rheumatoid arthritis). The therapeutic effect of mAbs is achieved by binding to their target antigen in the plasma or on the cell surface and **blocking deleterious receptor interactions** or triggering a **cytotoxic immune response** against abnormal cells.

A clinical trial is being conducted to evaluate the safety and efficacy of a novel therapy to treat refractory Crohn disease. The medication is a monoclonal antibody against the α4β7 integrin, which inhibits migration of T-lymphocytes into the intestinal parenchyma and produces a gut-selective anti-inflammatory effect. Patients who have active, moderate to severe Crohn disease and have failed conventional therapy are enrolled in the study. Many of these patients have renal or hepatic dysfunction, and some take other medications that affect cytochrome P450 enzymes. Which of the following is the most appropriate dose adjustment in this patient population to decrease drug toxicity?

- A. Higher dose in patients taking cytochrome P450 inducers
- B. Lower dose in patients with decreased glomerular filtration
- C. Lower dose in patients with hepatocellular dysfunction
- D. Lower dose in patients with renal tubular dysfunction
- E. No dose adjustment necessary

Submit

In both cases, tolerance can be innate or acquired. Innate tolerance refers to inborn differences in genes coding for enzymes involved in drug metabolism (pharmacokinetic) or receptor structure/expression (pharmacodynamic). Innate tolerance is apparent from the first dose, which elicits an unexpectedly weak effect. This patient experienced a good analgesic response initially, arguing against the presence of innate tolerance **(Choice A)**.

Acquired tolerance is defined as a decreased pharmacologic response following prolonged drug exposure. **Acquired pharmacodynamic tolerance** is the primary form of chronic opioid tolerance, characterized by downregulation and decreased responsivity (eg, GRK/beta-arrestin phosphorylation) of the mu opioid receptor system compared to the opioid-naïve state.

**(Choice C)** The kappa and delta opioid receptors bind to endogenous opioid-like neuropeptides (dynorphin and enkephalins, respectively) to mediate analgesia. Like mu receptors, they are also downregulated by chronic opioid administration, contributing further to acquired pharmacodynamic tolerance.

**(Choice D)** In acquired *pharmacokinetic* tolerance, altered ADME results in lower plasma drug levels. Higher rates of metabolism (eg, P450 enzyme autoinduction) can accelerate the inactivation/elimination of many medications (eg, methadone, carbamazepine). However, lower rates of excretion (eg, renal or hepatic insufficiency) would raise the plasma drug concentration, leading to potential overdose rather than tolerance.

**(Choice E)** Adiposity (eg, increasing obesity) can contribute to *pharmacokinetic* tolerance by raising the apparent volume of distribution, thereby lowering the plasma drug concentration. However, equilibration between plasma and extravascular compartments is complete within 5 drug half-lives, occurring long before this patient's development of tolerance after 3 months. Furthermore, adipose partitioning is primarily a concern for highly lipophilic drugs (eg, fentanyl, not oxycodone).

**Educational objective:**
Chronic opioid therapy leads to the development of acquired pharmacodynamic tolerance via downregulation and decreased responsiveness of opioid receptor systems.

This patient is receiving **chronic opioid therapy** for nonspecific low back pain due to lumbar osteoarthritis. He reports worsening pain despite an increased drug dose. No new structural explanation for increased pain was revealed on medical evaluation (ie, unchanged spine imaging and physical examination). Therefore, the loss of opioid analgesic efficacy is likely due to **drug tolerance**: higher doses of drugs are required to achieve the same clinical effect.

A distinction is drawn between pharmacokinetic versus pharmacodynamic tolerance:

- Pharmacokinetic tolerance (ADME): The plasma level of the active drug is decreased due to impaired **A**bsorption (eg, short bowel syndrome), increased tissue **D**istribution (eg, plasma protein binding, adiposity), increased **M**etabolism (eg, P450 cytochrome induction), or increased **E**xcretion.
- Pharmacodynamic tolerance: The plasma level of the active drug is unchanged (ie, normal pharmacokinetics). However, the action of the drug on target cells is blunted (eg, **receptor downregulation**, decreased intracellular signaling), reducing the overall pharmacologic effect.

In both cases, tolerance can be innate or acquired. Innate tolerance refers to inborn differences in genes coding for enzymes involved in drug metabolism (pharmacokinetic) or receptor structure/expression (pharmacodynamic). Innate tolerance is apparent from the first dose, which elicits an unexpectedly weak effect. This patient experienced a good analgesic response initially, arguing against the presence of innate tolerance **(Choice A)**.

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| Mechanisms of drug tolerance | | |
|---|---|---|
| **Tolerance** | **Mechanism** | **Example** |
| **Acquired pharmacokinetic** | • ADME: ↓ **A**bsorption, ↑ **D**istribution, or ↑ **M**etabolism & **E**xcretion (eg, enzyme induction)<br>• ↓ Plasma drug concentration relative to naïve state | • Rifampin (CYP3A4 inducer) accelerates metabolism of warfarin<br>• Carbamazepine induces its own metabolism after repeated dosing |
| **Acquired pharmacodynamic** | • ↓ Cellular response to drug (eg, receptor downregulation)<br>• Unchanged plasma drug concentration relative to naïve state | • Chronic opioid use: ↓ expression & responsivity of μ receptor system<br>• Frequent albuterol rescue inhaler: ↓ expression of airway β2 receptors |
| **Innate** | • Genetic (eg, polymorphisms) & epigenetic (eg, DNA methylation) differences<br>• Leads to pharmacokinetic or pharmacodynamic tolerance<br>• Tolerance apparent from first dose | • Slow metabolizer CYP2C19 allele: ↓ clopidogrel activation (↓ antiplatelet effect)<br>• Slow metabolizer CYP2D6 allele: ↓ codeine conversion to morphine (↓ analgesic effect) |
| **Behavioral (functional)** | • Ability to compensate for drug-induced impairment through learning & practice | • Maintaining appearance & mannerisms to appear nonintoxicated at work |

This patient is receiving **chronic opioid therapy** for nonspecific low back pain due to lumbar osteoarthritis. He reports worsening pain despite an increased drug dose. No new structural explanation for increased pain was

A 68-year-old man comes to the office due to worsening back pain. The patient has a history of severe lumbar degenerative disc disease that limits his daily activities. He declined surgery, and treatment with nonpharmacologic interventions and nonopioid analgesics have not adequately controlled the pain. The patient began taking long-acting oxycodone 5 months ago with good pain control. Over the past 2 months, he reports progressive worsening of the pain despite a modest increase in dose. The patient also takes acetaminophen for breakthrough pain and an osmotic laxative for constipation. Physical examination shows lower paraspinous tenderness but no lower extremity neurologic deficits. Spine imaging shows no significant changes from previous studies. Which of the following is the most likely reason for decreased analgesic efficacy in this patient?

- A. Innate tolerance due to genetic polymorphism of mu opioid receptors (3%)
- ✓ B. Pharmacodynamic tolerance due to decreased responsivity of the opioid receptor system (81%)
- ✗ C. Pharmacodynamic tolerance due to overexpression of delta and kappa opioid receptors (11%)
- D. Pharmacokinetic tolerance due to decreased rate of drug excretion (1%)
- E. Pharmacokinetic tolerance due to drug partitioning to the adipose tissue compartment (1%)

Incorrect
Correct answer
B

81%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

| Mechanisms of drug tolerance | | |
|---|---|---|
| **Tolerance** | **Mechanism** | **Example** |

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Submit

**marrow** (explaining this patient's **pancytopenia**).

**Folinic acid (leucovorin)** can reverse MTX toxicity if given early. It serves as a reduced form of folic acid thought **not** to require DHFR to be converted to THF and is therefore unaffected by MTX. Leucovorin is administered following high-dose MTX as part of a chemotherapeutic plan in which it serves to **rescue** bone marrow, and GI and other mucosal cells from MTX toxicity. In addition, when used in combination with 5-fluorouracil (**5-FU**), leucovorin **potentiates** the cytotoxic action of 5-FU (by binding thymidylate synthetase) and is frequently included in colorectal cancer chemotherapy regimens.

**(Choice A)** Allopurinol and its metabolite, oxipurinol, are predominantly noncompetitive inhibitors of xanthine oxidase. Allopurinol is used in the treatment of gout and for prevention of tumor lysis syndrome.

**(Choice B)** Amifostine is a cytoprotective free-radical scavenger used to decrease nephrotoxicity associated with platinum-containing and alkylating chemotherapeutic agents and to decrease xerostomia (dry mouth).

**(Choice C)** Dexrazoxane is an iron-chelating agent that can prevent anthracycline-induced cardiotoxicity.

**(Choice D)** Filgrastim is a granulocyte colony-stimulating factor analog used to stimulate the proliferation and differentiation of granulocytes in patients with neutropenia.

**(Choice F)** Mesna prevents hemorrhagic cystitis due to cyclophosphamide or ifosfamide. Mesna binds acrolein, the toxic metabolite formed by these agents.

**(Choice G)** Ondansetron (a serotonin 5-$HT_3$ receptor inhibitor) is used to treat nausea and vomiting following chemotherapy.

**Educational objective:**
Folinic acid (leucovorin) can reverse the toxicity of methotrexate in non-cancerous cells in the gastrointestinal mucosa and bone marrow if administered at the appropriate time. Leucovorin serves as a reduced form of folic acid that does not require the action of dihydrofolate reductase.

**Methotrexate** (MTX) is a folic acid analog that **inhibits dihydrofolate reductase** (DHFR), the enzyme that converts dietary folic acid to tetrahydrofolate (THF), through direct competition. THF is a single-carbon group donor in the synthesis of purines and thymidylic acid (which contributes to pyrimidine formation). MTX functions as a chemotherapeutic agent through **inhibition of DNA synthesis** and as an anti-psoriasis agent through immunomodulatory effects on activated T cells. However, MTX causes death of all **rapidly dividing** cells, particularly those of the **gastrointestinal tract** (GI) mucosa (explaining this patient's **aphthous ulcers**) and **bone marrow** (explaining this patient's **pancytopenia**).

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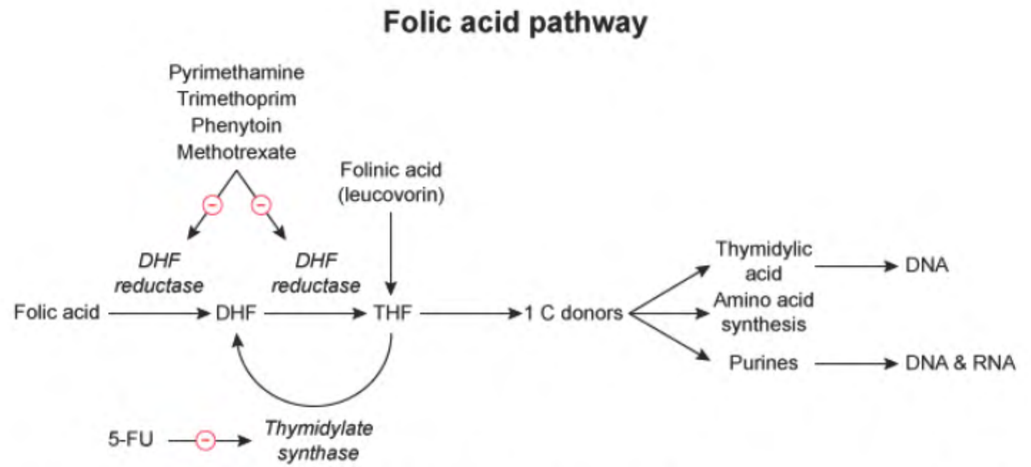


**5-FU** = 5-fluorouracil; **C** = carbon; **DHF** = dihydrofolate; **THF** = tetrahydrofolate. ©UWorld

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**Meth**
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**marrow** (explaining this patient's **pancytopenia**).

A 57-year-old man comes to the emergency department due to fevers and painful mouth ulcers. He recently began methotrexate therapy for psoriasis. However, the patient has mistakenly taken the medication daily instead of 3 times a week. His past medical history is also significant for hypertension and chronic kidney disease. Temperature is 38.1 C (100.6 F). Examination reveals multiple aphthous ulcers in the oral pharynx. A complete blood cell count is as follows:

| | |
|---|---|
| Hemoglobin | 10.4 g/dL |
| Platelets | 120,000/mm$^3$ |
| Leukocytes | 2,800/mm$^3$ |

Which of the following is the best next step in management?

- ✗ A. Allopurinol (3%)
- B. Amifostine (1%)
- C. Dexrazoxane (1%)
- D. Filgrastim (10%)
- ✓ E. Folinic acid (76%)
- F. Mesna (5%)
- G. Ondansetron (1%)

Incorrect
Correct answer
E

76%
Answered correctly

05 secs
Time Spent

2023
Version

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Submit

deactivate drugs and facilitate excretion from the body by improving water solubility. However, they also metabolize certain compounds to their active forms.

**Polymorphisms** may occur in the genes coding for these enzymes, altering their expression or activity. Three important phenotypes exist: **poor, intermediate, and rapid metabolizer**. Identifying these variations on an individual basis provides a framework for optimizing therapy, predicting treatment efficacy, and minimizing toxicity.

**Tamoxifen**, a selective estrogen receptor modulator used in the treatment of estrogen receptor-positive breast cancer, is a prodrug metabolized by CYP2D to its **active metabolite, endoxifen**. Patients with genetic polymorphisms resulting in poor CYP2D activity are exposed to decreased levels of the active metabolite and have a higher risk of disease relapse.

**(Choice A)** Activation of downstream signal transducer proteins, such as KRAS, leads to activation of transcription factors that promote cell growth. Mutations in the *KRAS* gene are associated with the development of colorectal and lung cancers.

**(Choice B)** Decreased activity of hepatic N-acetyltransferase results in a diminished ability to metabolize drugs such as isoniazid and sulfonamides, leading to an increased likelihood of toxicity.

**(Choice C)** Thiopurine methyltransferase is responsible for the metabolism of thiopurine compounds such as the immunosuppressive drug 6-mercaptopurine. Enzyme deficiency leads to increased drug toxicity.

**(Choice D)** P-glycoprotein is a cell membrane protein that drives efflux of a number of substances out of the cell. Overexpression of p-glycoprotein in tumor cells has been identified as a cause of multidrug resistance.

**Educational objective:**
Cytochrome P450 enzymes found in the liver are responsible for the majority of drug metabolism. Polymorphisms occurring in the genes coding for these enzymes result in various phenotypes that differ in their rates of metabolism; individual differences in phenotype alter treatment efficacy and drug toxicity.

**References**

**Cytochrome P450 (CYP) enzymes** are a group of heme-containing proteins that are responsible for the majority of **drug metabolism**, which occurs predominately in the liver. Various CYP subtypes exist, with CYP3A, CYP2D, and CYP2C as the most active subtypes involved in drug metabolism. These enzymes generally function to deactivate drugs and facilitate excretion from the body by improving water solubility. However, they also metabolize certain compounds to their active forms.

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**Educational objective:**
Cytochrome P450 enzymes found in the liver are responsible for the majority of drug metabolism. Polymorphisms

A researcher is conducting a retrospective study on breast cancer recurrence. Records of a number of patients with hormone receptor-positive, early-stage breast cancer who received adjuvant therapy with tamoxifen were evaluated. Various clinical, demographic, and drug concentration data were analyzed. A comparison of patients who had disease recurrence with those who remained cancer free showed that some of the relapsed patients had lower serum concentrations of endoxifen and 4-hydroxytamoxifen, the active metabolites of tamoxifen. Which of the following is the most likely cause of the drug's ineffectiveness in this subset of patients?

- A. Activating mutation affecting a downstream signal transducer (6%)
- ✗ B. Decreased hepatic N-acetyltransferase activity (15%)
- C. Deficiency of thiopurine methyltransferase enzyme (3%)
- D. Overexpression of P-glycoprotein in the tumor cells (10%)
- ✓ E. Polymorphism of a cytochrome P450 enzyme (63%)

Incorrect
Correct answer
E

63%
Answered correctly

24 secs
Time Spent

2023
Version

## Explanation

**Cytochrome P450 (CYP) enzymes** are a group of heme-containing proteins that are responsible for the majority of **drug metabolism**, which occurs predominately in the liver. Various CYP subtypes exist, with CYP3A, CYP2D, and CYP2C as the most active subtypes involved in drug metabolism. These enzymes generally function to deactivate drugs and facilitate excretion from the body by improving water solubility. However, they also metabolize certain compounds to their active forms.

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- E. Polymorphism of a cytochrome P450 enzyme

Submit

| | |
|---|---|
| Tachycardia | |

**Atropine** is an anticholinergic medication that can be administered prior to bronchoscopy to decrease respiratory mucus secretions and promote bronchodilation. **Anticholinergic** drugs competitively inhibit the muscarinic acetylcholine receptor both centrally (leading to delirium, coma, and respiratory failure) and peripherally (see toxidrome in table). The elderly are at particularly high risk of developing anticholinergic toxicity, likely due to decreased renal and hepatic clearance.

**Cholinesterase inhibitors** overcome this toxicity by inhibiting the degradation of acetylcholine, thereby increasing the concentration of acetylcholine at the synaptic cleft. Central nervous system (CNS) penetration and reversal of central symptoms are dependent on chemical structure:

- **Tertiary amines** (eg, **physostigmine**, galantamine, donepezil, rivastigmine) are lipophilic (nonpolar) and can easily cross the blood-brain barrier to reverse both central and peripheral symptoms.
- Quaternary amines (eg, neostigmine, edrophonium, pyridostigmine) are hydrophilic (polarized) and do not readily cross the blood-brain barrier. These drugs reverse peripheral symptoms only **(Choices B and D)**.

**(Choices A and C)** Both diazepam and haloperidol can be used for sedation or cases of severe agitation. Haloperidol is an antipsychotic that blocks dopamine receptors in the CNS, and diazepam is a long-acting benzodiazepine that positively modulates GABA-A activity. Neither medication reverses the peripheral anticholinergic manifestations (eg, mydriasis, tachycardia).

**Educational objective:**
Physostigmine is a cholinesterase inhibitor with a tertiary ammonium structure that can reverse both the central and peripheral nervous system symptoms of anticholinergic toxicity. Neostigmine, edrophonium, and pyridostigmine have a quaternary ammonium structure that limits central nervous system penetration.

| Pharmacology | Pharmacology (General Principles) | Anticholinergics |
|---|---|---|
| Subject | System | Topic |

| Anticholinergic toxicity | |
|---|---|
| **Symptom** | **Mechanism** |
| **"Hot as a hare"**<br>↑ Body temperature | • ↓ Sweating leads to ↓ heat dissipation |
| **"Dry as a bone"**<br>↓ Secretions (eg, mucous membranes, sweat glands) | • ↓ Glandular secretion & smooth muscle contraction |
| **"Red as a beet"**<br>Flushed skin | • Superficial vasodilation from ↑ body heat |
| **"Blind as a bat"**<br>Cycloplegia, mydriasis | • Paralysis of ciliary muscle & iris sphincter |
| **"Mad as a hatter"**<br>Altered mental status | • Permeates blood-brain barrier & affects CNS pathways |
| **"Full as a flask"**<br>Constipation, urinary retention | • ↓ Intestinal smooth muscle contraction<br>• ↓ Detrusor contraction & ↓ internal urethral sphincter relaxation |
| **"Fast as a fiddle"**<br>Tachycardia | • ↓ Vagal tone at the sinoatrial node |

A 78-year-old man was found to have a perihilar mass on screening CT scan. The patient's medical history is remarkable for chronic obstructive pulmonary disease, for which he takes albuterol inhalers as needed. He has smoked a pack of cigarettes daily for the last 50 years and does not drink alcohol or use illicit drugs. The patient is admitted for bronchoscopy and is premedicated with intramuscular atropine and becomes acutely restless, disoriented, and combative. Temperature is 38.1 C (100.5 F), blood pressure is 116/72 mm Hg, pulse is 110/min, and respirations are 15/min. Oxygen saturation is 99% on room air. On physical examination, his pupils are widely dilated and nonreactive to light. ECG shows sinus tachycardia. Which of the following agents will reverse all of this patient's signs and symptoms?

- A. Diazepam (4%)
- ✕ B. Edrophonium (8%)
- C. Haloperidol (2%)
- D. Neostigmine (13%)
- ✓ E. Physostigmine (72%)

Incorrect
Correct answer
E

72%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

| Anticholinergic toxicity | |
|---|---|
| **Symptom** | **Mechanism** |
| | |

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- D. Neostigmine
- E. Physostigmine

Submit

Drug dosing regimens are typically designed to maximize drug effectiveness and minimize toxicity. The above graph is comparing two different regimens with the same total dose (ie, 4 grams/24 hr) but with different dosing intervals (ie, 6 hr,12 hr). **Both regimens** have **similar trough levels** (ie, lowest concentration level before next dose) and maintain plasma levels above the bactericidal cutoff (eg, 15-20 µg/mL). As such, both regimens are likely to exhibit **similar efficacy**. However, **peak and average drug levels** are substantially **higher** with the **12-hour dosing regimen**. Because drug toxicity most often correlates with peak or average plasma drug levels, the **6-hour regimen** is likely to have **lower toxicity**.

**(Choice A)** Clearance (hepatic or renal) of a substance depends on the intrinsic properties of the agent. It is defined as the amount of plasma that is cleared of the drug over a given period (eg, mL/min). Drug clearance is typically the same regardless of the dosing schedule.

**(Choice B)** Average plasma drug levels are lower when a fixed amount of drug is given in more divided doses. In this example, 4 grams are administered every 24 hours, either in 2 doses (12-hr regimen) or 4 doses (6-hr regimen). Therefore, the more frequent 6-hour regimen would result in lower average plasma drug levels.

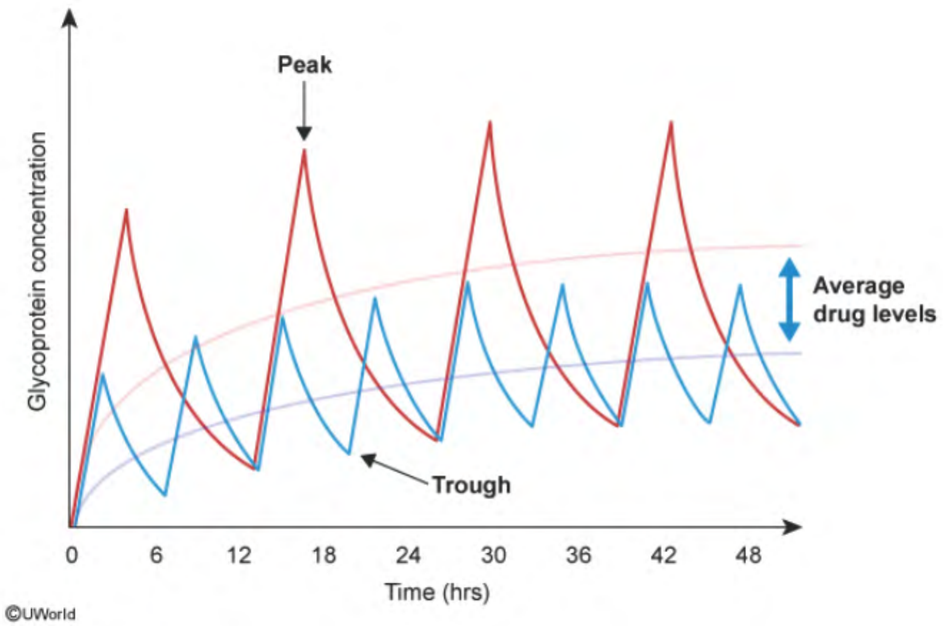
**(Choice C)** Patient compliance is increased when the frequency of dosing is minimized. Only 2 doses per day are needed with the 12-hour regimen; however, the 6-hour regimen needs 4 doses and is likely to be more disruptive to the patient's schedule.

**(Choice E)** The therapeutic window refers to the range of drug dosages that have an appropriate clinical effect. It begins at the lowest dose at which the drug is effective and ends at the highest dose without significant toxic effects. Drugs with a narrow therapeutic window are often dosed more frequently to prevent large swings in plasma concentration.

**Educational objective:**
Drug dosing regimens with more frequent dosing have lower peak and average drug levels, which can help reduce drug toxicity.

B. Higher average plasma drug levels (12%)

Exhibit Display

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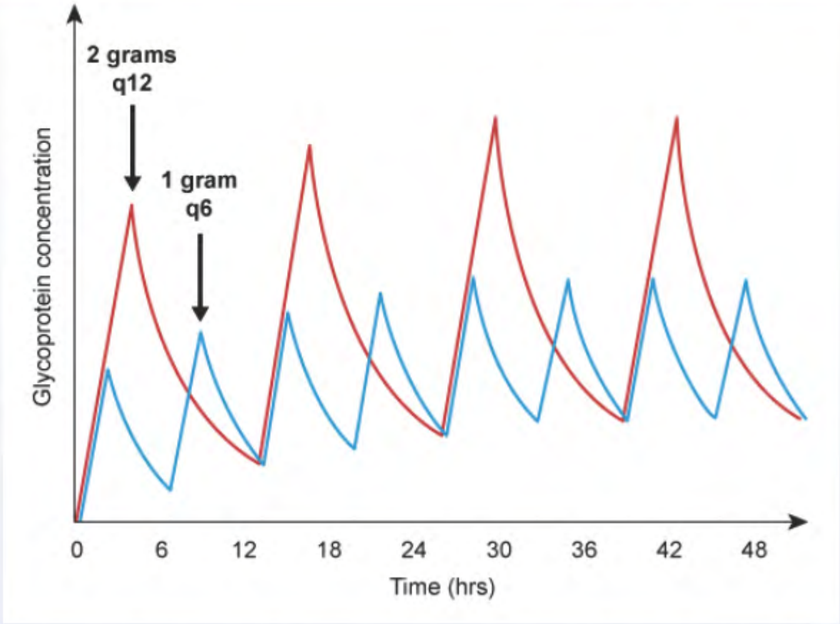



Compared to the 12-hour dosing regimen, the 6-hour regimen is most likely to exhibit which of the following features?

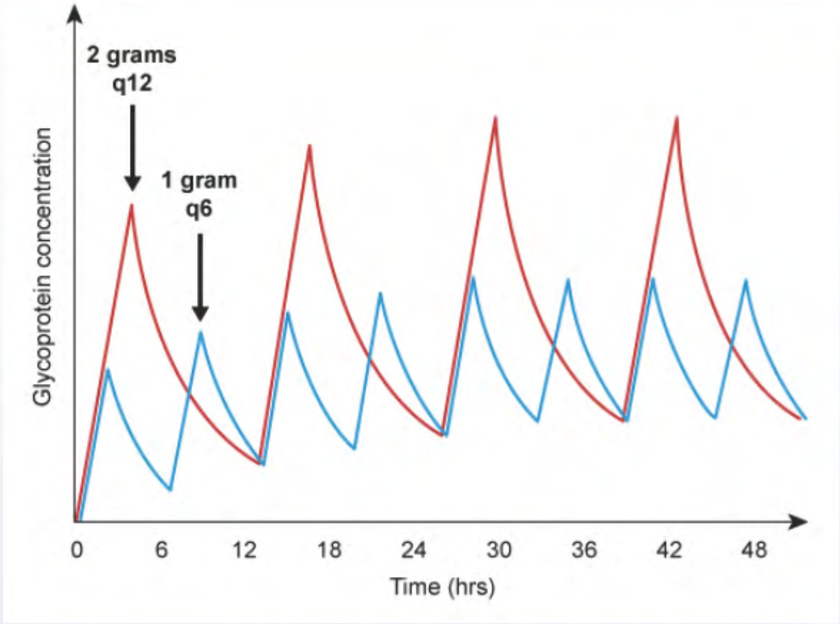
- A. Decreased renal clearance (4%)
- ✕ B. Higher average plasma drug levels (12%)
- C. Improved patient compliance (2%)
- ✓ D. Lower drug toxicity (69%)
- E. Narrower therapeutic window (10%)

Incorrect
Correct answer
D

69%
Answered correctly

09 secs
Time Spent

2023
Version

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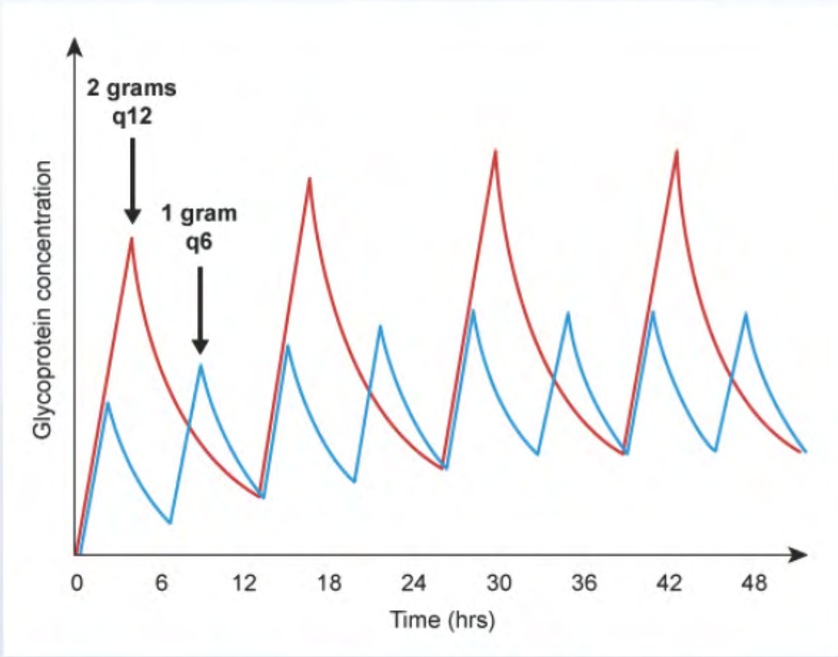
- B. Higher average plasma drug levels
- C. Improved patient compliance
- D. Lower drug toxicity
- E. Narrower therapeutic window

Submit

Researchers are developing a new glycopeptide antibiotic similar to vancomycin. Susceptibility testing reveals that the new drug is bactericidal against gram-positive organisms at serum concentrations above 15 µg/mL. Two different dosage regimens are developed to achieve a target serum trough concentration of 15-20 µg/mL: one administered as 1 gram every 6 hours and the other as 2 grams every 12 hours. The two regimens are tested in healthy volunteers during an early-phase clinical trial, and the following pharmacokinetic profiles are obtained.

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- A. Decreased renal clearance
- B. Higher average plasma drug levels

Bioavailability is the fraction of an administered drug that reaches the systemic circulation unchanged. **Oral bioavailability** depends on the drug's intrinsic ability to be absorbed by the gastrointestinal mucosa (eg, poor with vancomycin) and its propensity for metabolization by intestinal and **hepatic enzymes** (first-pass metabolism).

When a drug has high **first-pass metabolism**, large amounts of its metabolites (rather than the drug itself) enter the systemic circulation. Drugs that are largely inactivated by first-pass metabolism (ie, low oral bioavailability) are often administered by a route that bypasses the portal circulation (eg, intravenous, sublingual).

**Rectal administration** (via suppository) allows a drug to **partially escape** first-pass metabolism. Venous drainage of the anorectum above the dentate line is to the portal venous system via the superior rectal veins (which drain to the inferior mesenteric vein). However, the region **below the dentate line** drains into the systemic circulation via the middle and inferior rectal veins (which drain to the internal iliac and internal pudendal veins, respectively). For a drug that is inactivated by first-pass metabolism, the rectal route allows a higher proportion of the drug to bypass portal circulation, increasing bioavailability.

**(Choices B, C, and D)** For orally administered drugs, the small intestine is a major site of absorption owing to its large surface area and high blood flow rates. In contrast, the rectum has a much smaller surface area, lower blood flow rates, and often contains absorptive stool. Therefore, rectally administered drugs are typically absorbed more slowly and erratically compared to orally administered drugs.

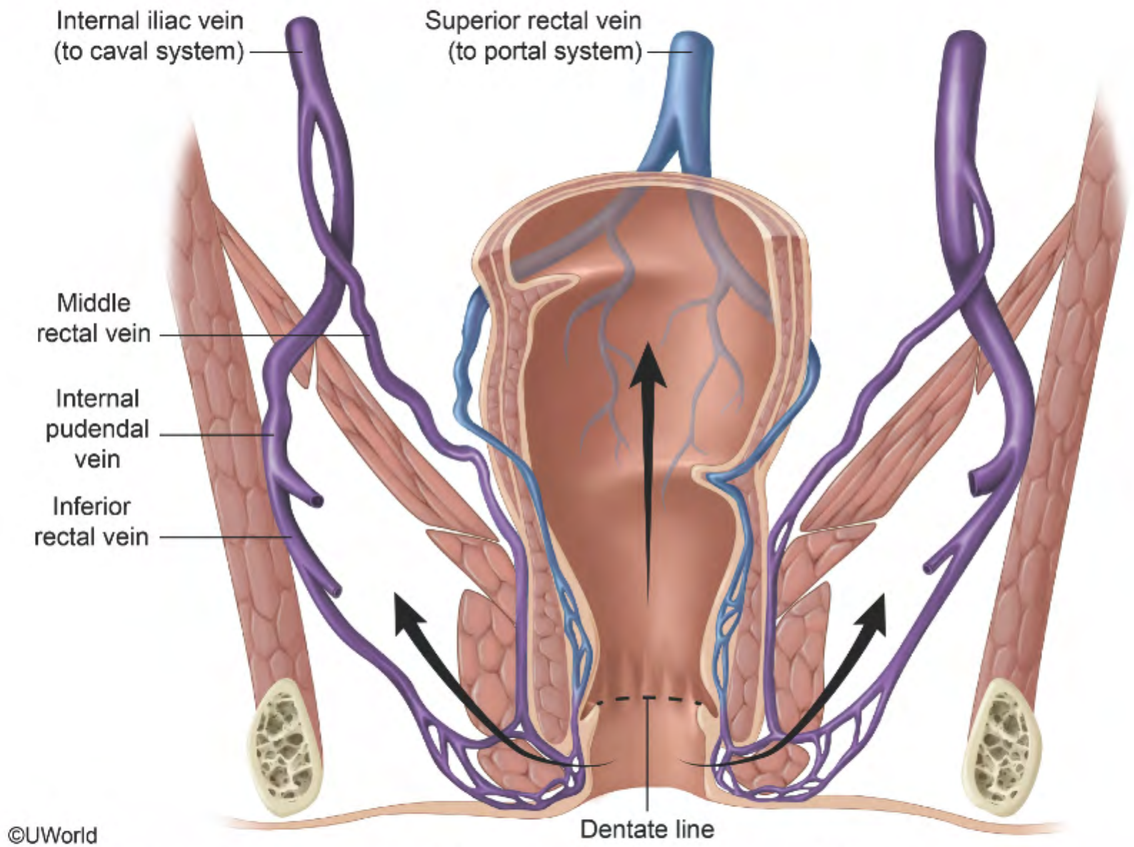
**(Choice E)** Reduced renal blood flow causes a decrease in the glomerular filtration rate (GFR), which in turn slows elimination of renally excreted drugs (ie, increases bioavailability). Patients with reduced GFR may require a lower dose to prevent adverse effects. However, the route of administration does not impact drug clearance.

**Educational objective:**
Drugs administered orally must pass through the portal circulation and are subject to first-pass metabolism by intestinal and hepatic enzymes. Rectal administration is capable of partially bypassing first-pass metabolism due to the portion of venous outflow that goes directly to the systemic circulation; drugs with extensive first-pass metabolism have increased bioavailability when administered rectally.

Internal iliac vein (to caval system)
Superior rectal vein (to portal system)

Exhibit Display

## Anorectal venous drainage

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**Rectal administration** (via suppository) allows a drug to **partially escape** first-pass metabolism. Venous

A group of investigators is conducting a phase I clinical trial for a newly developed synthetic opioid. After several volunteers ingest a fixed oral dose, the plasma concentrations of the active drug and its inactive metabolites are measured. The plasma concentration of the drug is determined to be subtherapeutic. After rectal administration of the same dose of the drug, the peak drug plasma concentration is almost double the level measured after oral administration. Which of the following best accounts for the observed difference in the concentration of the active drug?

- ✓ A. Decreased drug delivery to the liver (70%)
- ✗ B. Greater blood flow to the rectum (4%)
- C. Increased rectal absorption rate (20%)
- D. Larger rectal surface area (2%)
- E. Reduced renal blood flow (1%)

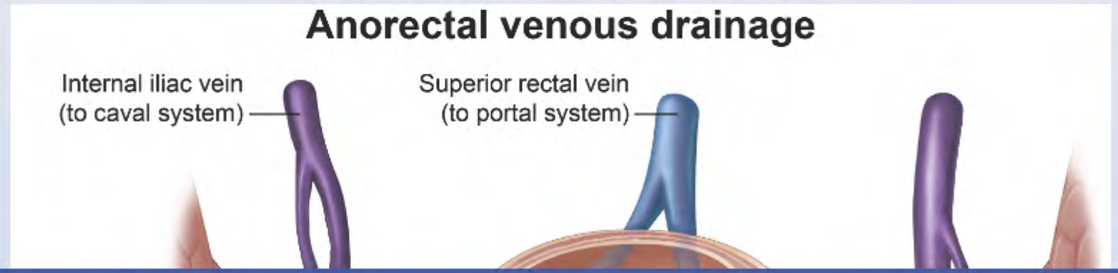
Incorrect
Correct answer
A

70%
Answered correctly

04 secs
Time Spent

2023
Version

Explanation



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- A. Decreased drug delivery to the liver
- B. Greater blood flow to the rectum
- C. Increased rectal absorption rate
- D. Larger rectal surface area
- E. Reduced renal blood flow

Submit

reduced intestinal motility) can have a variable effect on the absorption of orally administered drugs. However, in this case, the drug is being administered **intravenously**, so changes in absorption are unlikely to be the cause of the plasma concentration discrepancy.

**Neonates** also have an **increased** proportion of **total body water** with a lower content of body fat compared to adults. This difference in body composition results in **water-soluble drugs** (eg, aminoglycosides, vancomycin) having a **larger than expected volume of distribution** relative to body mass, leading to **lower plasma concentrations** when the drug is administered at the same weight-based dosage as given to adult patients. Furthermore, neonates have an immature blood-brain barrier that increases the permeability of many substances into the CNS compartment, which (in addition to increasing the distribution volume) can increase the risk of CNS toxicity.

**(Choice A)** The liver is not fully developed in neonates and has decreased expression of drug-metabolizing enzymes (eg, cytochrome P450 isoenzymes, glucuronidation enzymes). This can lead to decreased clearance of drugs that are hepatically metabolized (eg, acetaminophen, morphine). However, this would result in increased (not decreased) plasma drug levels.

**(Choice B)** Renal blood flow and glomerular filtration rate are decreased in neonates compared to adults. For drugs that are renally excreted, reduced renal clearance would cause increased serum drug concentrations, potentially leading to toxicity. However, in this study the serum concentration is lower in neonates than in adults.

**(Choice C)** Neonates have decreased (not increased) plasma protein concentrations compared to adults, which can increase free levels of highly protein-bound drugs (eg, phenytoin, penicillin). Elevated bilirubin levels in neonates can further increase the concentration of unbound drug by displacing them from albumin binding sites.

**Educational objective:**
Neonates have a higher proportion of body water compared to adults. This can result in lower plasma concentrations of water-soluble drugs if they are administered at the same weight-based dosage as given to adult patients.

| | | |
|---|---|---|
| | • Blood-brain barrier immaturity | • ↑ CNS toxicity |
| **Metabolism** | • ↓ CYP enzyme activity<br>• ↓ Hepatic glucuronidation | • ↑ Sensitivity to hepatically metabolized drugs |
| **Elimination** | • ↓ Renal blood flow & GFR | • May require lower doses of renally excreted drugs |
| **CYP** = cytochrome P450; **GFR** = glomerular filtration rate. | | |

In this example, a novel glycopeptide antibiotic is administered to adult and neonatal patients using the **same weight-based dosing regimen** (eg, 5 mg/kg). However, plasma concentrations of the drug are lower in **neonates** compared to the adults, resulting in **decreased effectiveness**.

Neonates have substantial pharmacokinetic differences compared to adult patients that affect drug absorption, distribution, and elimination. Changes in gastrointestinal parameters in neonates (eg, decreased gastric pH, reduced intestinal motility) can have a variable effect on the absorption of orally administered drugs. However, in this case, the drug is being administered **intravenously**, so changes in absorption are unlikely to be the cause of the plasma concentration discrepancy.

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| Pharmacokinetic differences between neonatal patients and adults | | |
|---|---|---|
| | **Altered parameters** | **Clinical effects** |
| **Distribution** | • ↑ Proportion of body water<br>• Blood-brain barrier immaturity | • ↑ Distribution of water-soluble drugs may necessitate higher mg/kg dose<br>• ↑ CNS toxicity |
| **Metabolism** | • ↓ CYP enzyme activity<br>• ↓ Hepatic glucuronidation | • ↑ Sensitivity to hepatically metabolized drugs |
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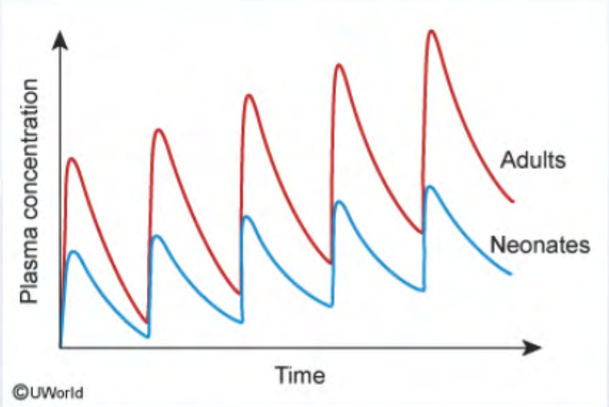
Researchers develop a novel glycopeptide antibiotic similar to vancomycin that is bactericidal against many gram-positive bacteria. From animal studies, they determine that the effective drug dosage is 5 mg/kg/day administered intravenously in divided doses. In a clinical trial, the antibiotic is administered to adult and neonatal patients with gram-positive infections. The drug is found to be effective in adults but not in neonates. During further analysis, plasma concentrations of the drug are measured in both groups, with the results shown in the image below:




Compared to adults, which of the following neonatal factors is the most likely cause of the difference in drug effectiveness?

- A. Decreased cytochrome P450 activity (25%)
- ✗ B. Decreased renal blood flow (3%)
- C. Elevated plasma protein level (26%)
- ✓ D. High body water content (43%)

Incorrect
Correct answer
D

43%
Answered correctly

06 secs
Time Spent

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Version

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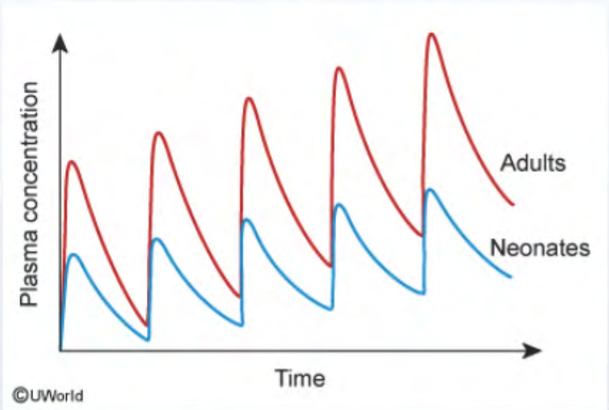


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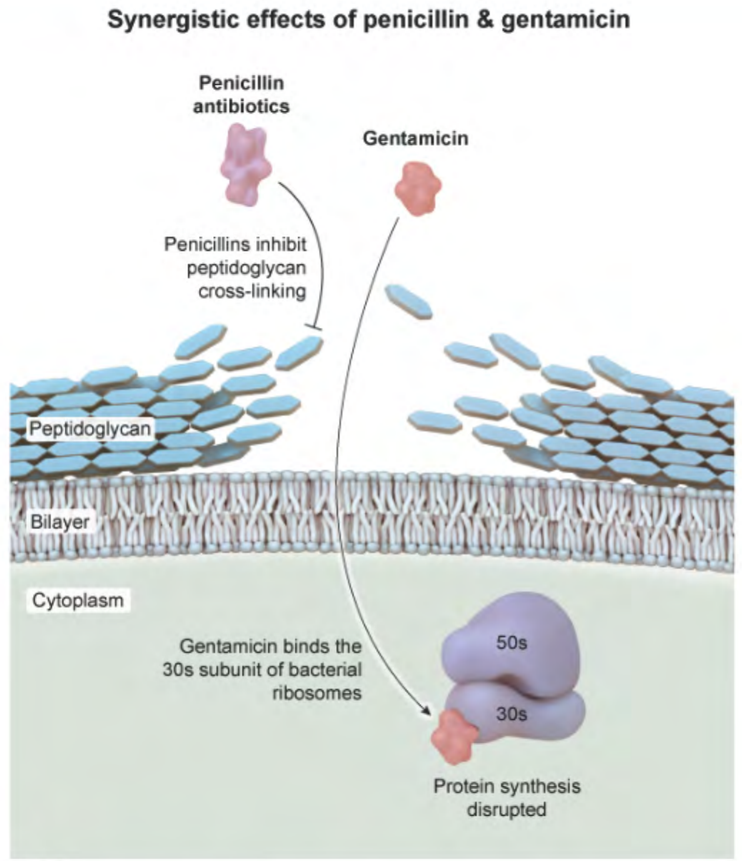


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necessary for the formation of tetrahydrofolate (THF), a cofactor needed for synthesis of **purine nucleic acids**. Sulfadiazine inhibits **dihydropteroate synthase**, a microbial enzyme that generates dihydropteroate, which is converted to dihydrofolic acid. Pyrimethamine inhibits **dihydrofolate reductase**, an enzyme that converts dihydrofolic acid to THF.

Sulfadiazine does not impair host DNA synthesis because dihydropteroate synthase is not found in human cells. In contrast, pyrimethamine partially impairs host DNA synthesis because dihydrofolate reductase generates THF in host cells. However, **leucovorin** (folinic acid), a derivative of THF that does not require conversion by dihydrofolate reductase, is usually administered with pyrimethamine to provide a bypass substrate for the generation of host purine nucleic acids.

**(Choice A)** Patients are often treated with 2 different classes of antimicrobial medications to broaden the coverage of potential pathogens. Sulfadiazine and pyrimethamine both block the same metabolic pathway, so the combination is less useful for empiric antimicrobial therapy.

**(Choice B)** Gentamicin is often administered with an agent that targets the bacterial cell wall (eg, ampicillin, vancomycin) to allow gentamicin to enter the intracellular space. Use of sulfadiazine with pyrimethamine does not alter intracellular penetration.

**(Choice C)** Bacterial resistance can occur due to the production of an inactivating enzyme (eg, beta-lactamase). Administration of an agent that inhibits the enzyme (eg, clavulanic acid) can often restore the effect of the antibiotic (eg, amoxicillin).

**(Choice D)** Probenecid blocks the renal tubular excretion of most beta-lactam antibiotics, which can increase their serum level. Sulfadiazine and pyrimethamine are not used together to alter renal excretion.

**Educational objective:**
Congenital toxoplasmosis is treated with sulfadiazine plus pyrimethamine. These medications work synergistically to inhibit formation of tetrahydrofolate, a necessary cofactor for purine nucleotide synthesis.

Methionine

**DHFR** = dihydrofolate reductase; **MTX** = methotrexate; **THF** = tetrahydrofolic acid; **TMP** = trimethoprim. ©UWorld

***Toxoplasma gondii*** is a ubiquitous protozoan that rarely causes illness in healthy individuals but can cause severe infection in immunocompromised patients or those with **congenital infection**. Symptomatic congenital disease is often marked by intracranial calcification, hydrocephalus, chorioretinitis, jaundice, and/or thrombocytopenia. Early treatment with **sulfadiazine and pyrimethamine** reduces neurologic and retinal sequelae.

Sulfadiazine and pyrimethamine work **synergistically** to **inhibit protozoal DNA synthesis** by blocking 2 steps necessary for the formation of tetrahydrofolate (THF), a cofactor needed for synthesis of **purine nucleic acids**. Sulfadiazine inhibits **dihydropteroate synthase**, a microbial enzyme that generates dihydropteroate, which is converted to dihydrofolic acid. Pyrimethamine inhibits **dihydrofolate reductase**, an enzyme that converts dihydrofolic acid to THF.

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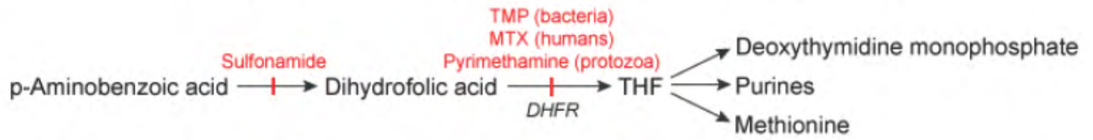
**(Choice C)** Bacterial resistance can occur due to the production of an inactivating enzyme (eg, beta-lactamase).

reason for using multiple drugs during this patient's treatment?

Exhibit Display

**Trimethoprim-sulfamethoxazole & folic acid pathway**

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Sulfadiazine and pyrimethamine work **synergistically to inhibit protozoal DNA synthesis** by blocking 2 steps

A boy is delivered via spontaneous vaginal delivery at 39 weeks gestation to a woman, gravida 1 para 0. The boy is vigorous with a strong cry, requiring no interventions after delivery except for warming and drying. APGAR scores are 8 and 9 at 1 and 5 minutes, respectively. Head circumference measures <10th percentile, and the placenta has numerous calcifications. Serology is consistent with congenital toxoplasmosis. As part of treatment, he is prescribed a combination of pyrimethamine and sulfadiazine. Which of the following best describes the reason for using multiple drugs during this patient's treatment?

- A. Broader spectrum of coverage (5%)
- ✗ B. Enhanced intracellular drug penetration (14%)
- C. Enzymatic inhibition of an inactivating enzyme (10%)
- D. Reduced urinary excretion of active metabolites (3%)
- ✓ E. Synergistic reduction of DNA synthesis (66%)

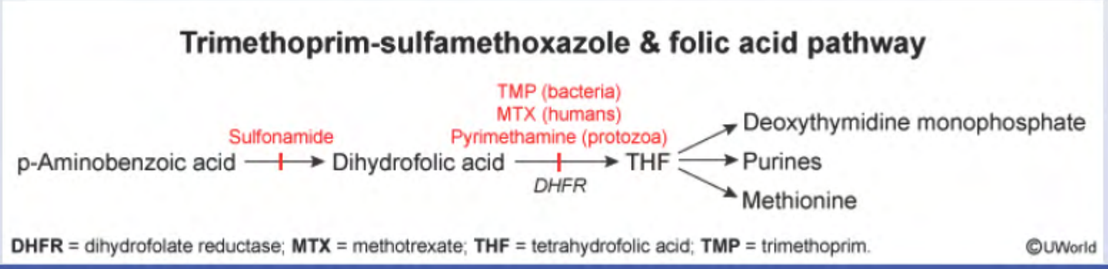
Incorrect
Correct answer
E

66%
Answered correctly

06 secs
Time Spent

2023
Version

Explanation



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- C. Enzymatic inhibition of an inactivating enzyme
- D. Reduced urinary excretion of active metabolites
- E. Synergistic reduction of DNA synthesis

Submit


Drug distribution is not uniform; the rate at which drugs are delivered to target tissues is dependent on several factors, such as regional blood flow and drug characteristics. The pharmacokinetic profile of highly lipophilic anesthetic drugs, such as propofol, can be predicted using a **multi-compartment** model of distribution. Following administration of a single intravenous bolus, drug levels are high in the **central compartment** (ie, plasma). However, the drug is quickly distributed to the **well-perfused peripheral compartment** (eg, brain, liver, kidneys, lungs) due to the increased lipophilicity of the tissues compared to the blood.

Over time, drug **redistribution** will occur through the central compartment into the **poorly-perfused peripheral compartment** (eg, skeletal muscle, fat, bone), which has the highest volume of distribution for lipophilic agents. Redistribution occurs rapidly with highly lipophilic drugs and is responsible for the short duration of action seen with commonly used anesthetics such as **propofol**.

**(Choices A, B, C, and D)** These organs have relatively high blood flow and are considered part of the well-perfused peripheral compartment. They will rapidly take up drugs from the central compartment and are visualized as the dashed line on the above graph.

**Educational objective:**
Following intravenous administration, a highly lipophilic drug will be rapidly distributed to organs with high blood flow (eg, brain, liver, kidneys, lungs). The drug is then redistributed to tissues with relatively lower blood flow (eg, skeletal muscle, fat, bone). This accounts for the short duration of action of many commonly used anesthetics, such as propofol.

| Pharmacology | Pharmacology (General Principles) | Anesthesia |
|---|---|---|
| Subject | System | Topic |

Incorrect
Correct answer

43%
Answered correctly

46 secs
Time Spent

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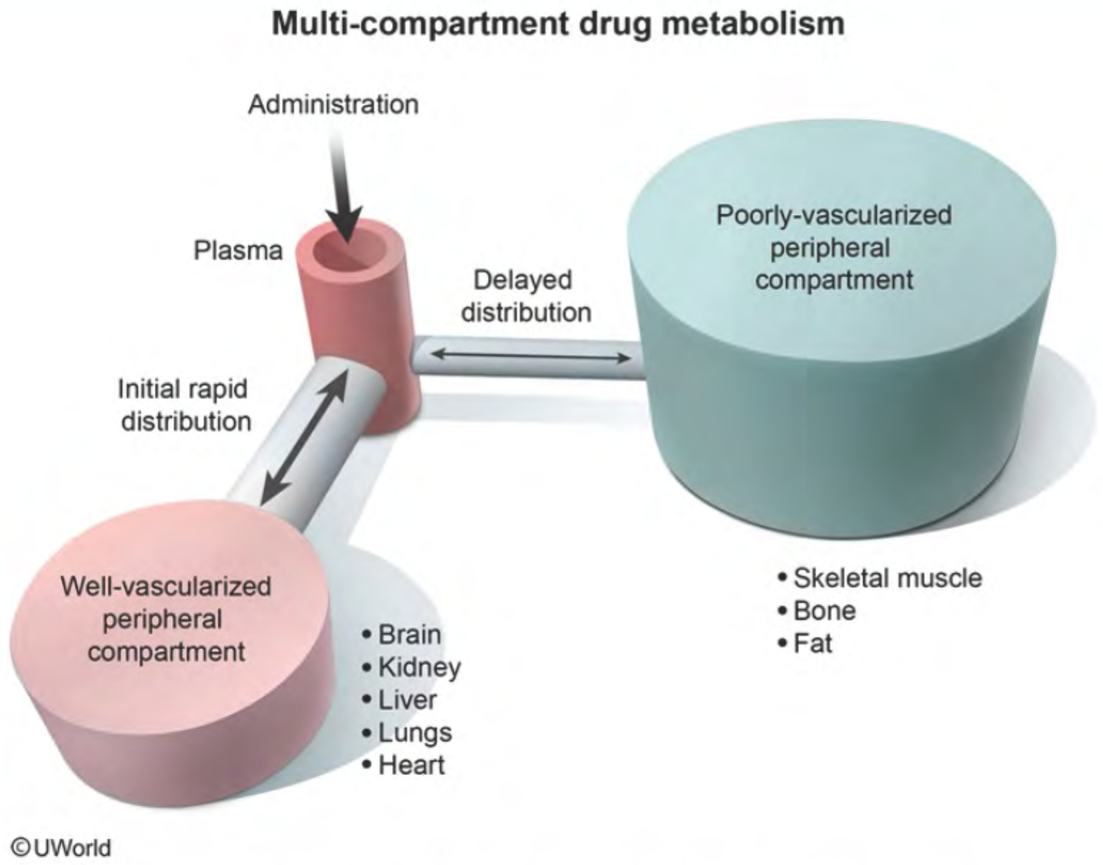


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Drug
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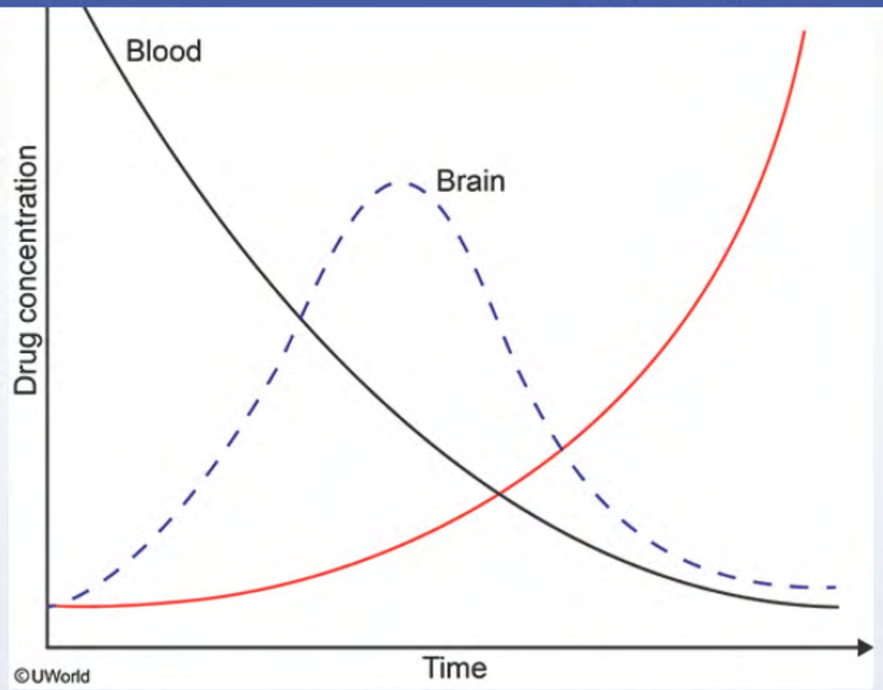


The red line on the graph most likely corresponds to which of the following tissues?

- A. Heart (1%)
- B. Kidney (18%)
- ✗ C. Liver (29%)
- D. Lungs (6%)
- ✓ E. Skeletal muscle (43%)

Incorrect
Correct answer
E

43%
Answered correctly

46 secs
Time Spent

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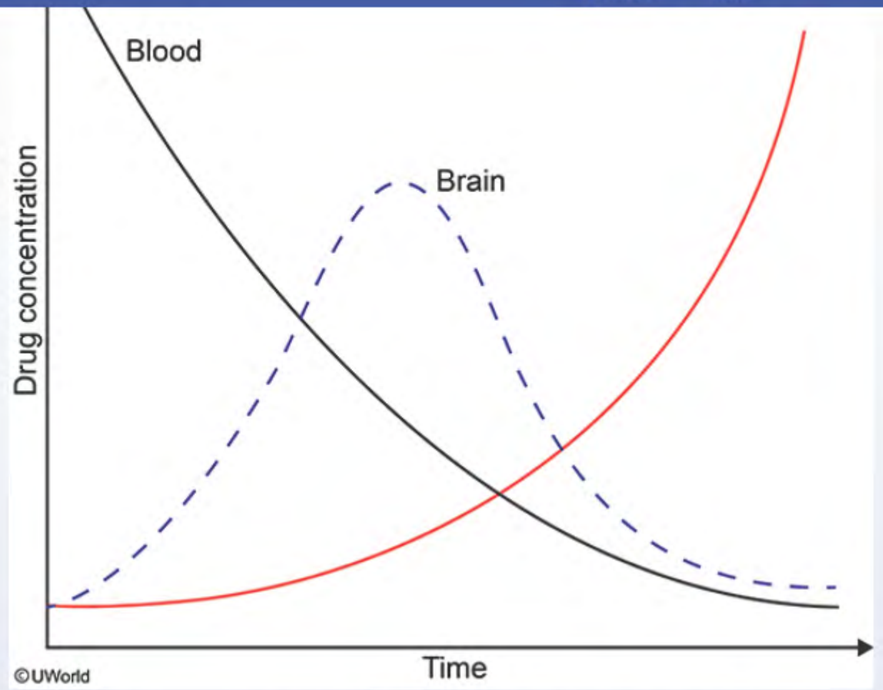


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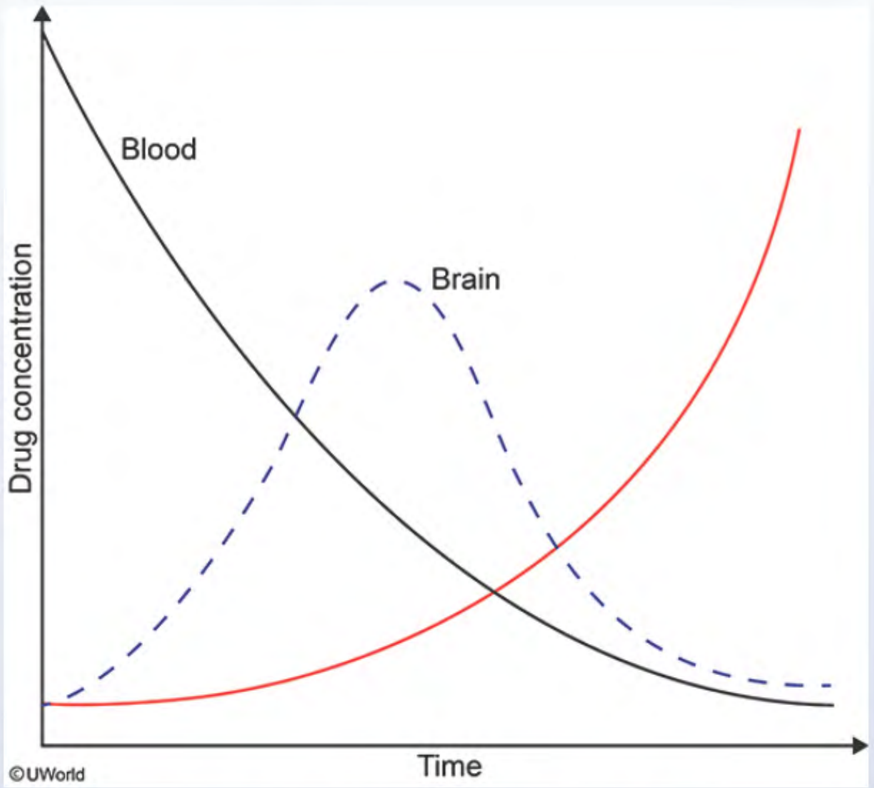
- E. Skeletal muscle

Submit

A group of investigators is studying the pharmacokinetic properties of the anesthetic drug propofol. A radiolabeled formulation of the drug is prepared and a single bolus is administered to adult guinea pigs. Blood and tissue samples are then collected at predetermined time intervals. Concentrations of the radioactive drug in the samples are assessed by liquid scintillation counting. The graph below demonstrates the drug concentration-time relationship in various tissues.




The red line on the graph most likely corresponds to which of the following tissues?

A. Heart

common and persistent opioid side effect.

Opioids stimulate mu receptors in the gastrointestinal tract, causing decreased secretions and gastric motility. Normal bowel function rarely resumes. Patients who require prolonged opioid therapy should receive a **prophylactic bowel regimen** (increased fluid intake, dietary fiber, and laxatives) to minimize constipation.

**(Choice A)** Opioids can produce significant euphoria, mood alterations, and rewarding pleasurable effects. The mechanism of euphoria and rewarding properties may involve dopaminergic pathways in the nucleus accumbens. Tolerance to euphoric effects develops rapidly, underlying the addictive potential of this medication class.

**(Choice B)** In most cases, opioid-induced pruritus is mild and tolerance develops.

**(Choice C)** Nausea with or without vomiting is a common side effect during initiation of opioid therapy, but tolerance develops within days and persistent nausea is uncommon. Opioids stimulate the chemoreceptor trigger zone, leading to emesis.

**(Choice D)** Respiratory depression is the most serious, yet rare, side effect of opioid therapy. Opioids depress respiration by reducing responsiveness of brainstem respiratory centers to increased levels of carbon dioxide. Patients who take opioids regularly are unlikely to develop respiratory depression as tolerance to this side effect develops rapidly.

**(Choice E)** Sedation typically occurs during initiation of therapy and usually disappears after several days. It is not unusual for patients to be drowsy and sleep more during the first days of therapy.

**(Choice F)** Opioids block urinary voiding reflexes and also increase sphincter tone and bladder volume. This results in an antidiuretic effect and urinary retention. Tolerance to these effects develops rapidly.

**Educational objective:**
Chronic opioid use leads to the development of tolerance to analgesic effects and most side effects, with the exception of constipation and miosis. To prevent bowel complications, it is recommended that patients be treated prophylactically with adequate fluid intake and daily laxatives.

Opioid therapy is the first-line treatment for chronic cancer pain, with effective management commonly requiring higher doses over prolonged periods. An increase in dosage is often necessary to maintain adequate pain control following the development of tolerance to analgesic effects. Tolerance to most opioid side effects is also expected to occur. However, tolerance to constipation and miosis does not readily occur, and **constipation** is the most **common** and **persistent opioid side effect**.

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A 55-year-old woman is diagnosed with metastatic breast cancer. The patient is treated with an opioid analgesic for bone pain that is well controlled during the first week of therapy. The following week, the analgesic dose becomes ineffective and the patient reports nausea, itching, and constipation. She has become very weak and is unable to walk due to the pain. The opioid dose is increased. The patient is concerned about side effects with higher dosages, noting that her son has a history of opioid dependence, and "I watched him suffer a lot of bad reactions." The physician explains the concept of tolerance to opioids and that high doses are commonly required to control pain. Over the next few weeks, the patient would likely experience which of the following?

- A. Euphoria (4%)
- B. Increased itching (1%)
- ✗ C. Persistent nausea and vomiting (2%)
- D. Respiratory depression (10%)
- E. Sedation (6%)
- F. Urinary retention (1%)
- ✓ G. Worsening constipation (73%)

Incorrect
Correct answer
G

73%
Answered correctly

04 secs
Time Spent

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Version

Explanation

Opioid therapy is the first-line treatment for chronic cancer pain, with effective management commonly requiring higher doses over prolonged periods. An increase in dosage is often necessary to maintain adequate pain control

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- C. Persistent nausea and vomiting
- D. Respiratory depression
- E. Sedation
- F. Urinary retention
- G. Worsening constipation

Submit

binding of **arrestin**, a protein that prevents further G protein activation and links the receptor complex to clathrin, facilitating receptor endocytosis and depletion from the cell surface.

As alpha-adrenergic receptors become increasingly scarce along the blood vessels of the nasal mucosa, the release of endogenous catecholamines is no longer sufficient to provide adequate vasoconstrictive stimulation. The resulting congestion/rhinorrhea can be relieved only with **increasing doses** of exogenous alpha agonists. Treatment involves **cessation** of the culprit decongestant, sometimes with use of intranasal corticosteroids to relieve severe symptoms.

**(Choice A)** Accelerated drug metabolism can lead to tolerance when a substance induces the enzymes responsible for its degradation (ie, cytochromes P450). This mechanism is responsible for the tolerance seen with ethanol and barbiturates.

**(Choice B)** Decreased receptor affinity due to intracellular domain modification (eg, phosphorylation) can play a role in receptor desensitization. However, desensitization of adrenergic receptors is better explained by the decoupling of G proteins (which are blocked by arrestins) and subsequent receptor internalization.

**(Choice C)** Tolerance to adrenergic agonists develops due to the binding of arrestins to stimulated adrenergic receptors, preventing G proteins from interacting with the receptor. G proteins themselves do not become depleted during this process.

**(Choice E)** Parasympathetic stimulation of the nasal mucosa causes vasodilation, increases plasma extravasation, and stimulates glandular mucous secretion. Patients with rhinitis medicamentosa have increased parasympathetic tone (physiologic antagonism) that contributes to the congestion/rhinorrhea.

**Educational objective:**
Activation of adrenergic receptors results in arrestin binding and receptor internalization. This effect is responsible for the tolerance effect seen with alpha-adrenergic (eg, decongestants, vasopressors) and beta-adrenergic (eg, bronchodilators) agonists.

| Example mechanisms of tachyphylaxis | |
|---|---|
| Adrenergic agonists | Receptor inactivation & internalization by arrestins |
| Indirect sympathomimetics | Depletion of catecholamines from nerve terminals |
| Nitrates | Depletion of reduced thiols decreases mtALDH activity & NO production |
| Desmopressin (vWD) | Depletion of vWF from endothelial storage sites |
| Barbiturates | Induction of CYP450 enzymes |

**CYP450** = cytochrome P450; **mtALDH** = mitochondrial aldehyde dehydrogenase; **NO** = nitric oxide; **vWD** = von Willebrand disease; **vWF** = von Willebrand factor.

This patient has rhinitis medicamentosa due to the use of a nasal decongestant spray containing an **alpha-adrenergic agonist** (eg, oxymetazoline). Intranasal application of alpha agonists induces vasoconstriction of superficial blood vessels in the nasal mucosa, reducing rhinorrhea and congestion. Although these agents are highly effective for symptom control, use for more than a few days is associated with **rebound rhinitis** and dosage escalation due to **tachyphylaxis**.

Tolerance to alpha-adrenergic decongestants develops quickly due to **receptor internalization**. Both alpha- and beta-adrenergic receptors undergo a conformational change on ligand binding, allowing them to activate heterotrimeric G proteins involved in signal transduction. However, the change in conformation also results in the binding of **arrestin**, a protein that prevents further G protein activation and links the receptor complex to clathrin, facilitating receptor endocytosis and depletion from the cell surface.

As alpha-adrenergic receptors become increasingly scarce along the blood vessels of the nasal mucosa, the release of endogenous catecholamines is no longer sufficient to provide adequate vasoconstrictive stimulation. The resulting congestion/rhinorrhea can be relieved only with **increasing doses** of exogenous alpha agonists. Treatment involves **cessation** of the culprit decongestant, sometimes with use of intranasal corticosteroids to

A 31-year-old man comes to the office due to persistent nasal congestion and rhinorrhea. The patient has a history of allergic rhinitis and recently moved across the country to start a new job. His nasal symptoms worsened after the move, and he started using an over-the-counter intranasal decongestant spray that initially provided prompt relief. However, after a few days, he had to increase the frequency and number of sprays per nostril needed for adequate symptom control. On examination, the nasal turbinates are swollen and pale with a clear nasal discharge. Which of the following mechanisms is most likely responsible for this patient's increased medication use?

- A. Accelerated drug metabolism (4%)
- ✗ B. Decreased receptor affinity (31%)
- C. Depletion of receptor-associated G proteins (12%)
- ✓ D. Increased receptor internalization (48%)
- E. Reduced parasympathetic activity (3%)

Incorrect
Correct answer
D

48%
Answered correctly

06 secs
Time Spent

2023
Version

Explanation

| Example mechanisms of tachyphylaxis | |
|---|---|
| Adrenergic agonists | Receptor inactivation & internalization by arrestins |
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- C. Depletion of receptor-associated G proteins
- D. Increased receptor internalization
- E. Reduced parasympathetic activity

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depression (eg, **somnolence**, coma). Morphine is primarily metabolized by the liver via glucuronidation to form **2 major metabolites**. These metabolites, morphine-3-glucoronide and **morphine-6-glucoronide**, then undergo **renal elimination** via excretion in the urine. Because the metabolites are metabolically active, **renal dysfunction** can lead to **metabolite accumulation** and opioid toxicity. Morphine-6-glucoronide is particularly responsible for toxicity, acting as a more potent mu opioid receptor agonist than morphine itself.

Due to its metabolically active and renally cleared metabolites, morphine requires careful monitoring when used in patients with renal dysfunction. When opioid pain control is needed in such patients, fentanyl or hydromorphone is often preferred as these drugs are predominantly hepatically cleared.

**(Choice A)** Decreased first-pass metabolism occurs with drugs that are given by a route other than orally, allowing the drug to reach the systemic circulation without passing through the portal circulation and the liver. Examples include drugs that are administered sublingually, rectally, or intravenously.

**(Choice B)** Decreased hepatic metabolism is common in the elderly or in patients with advanced liver disease (eg, cirrhosis). Although this patient has metastatic disease to the liver, accumulation of morphine metabolites is a more likely cause of toxicity in the setting of known renal failure.

**(Choice C)** Enterohepatic circulation occurs when a drug undergoes biliary excretion into the small intestine, where it is then reabsorbed back into the bloodstream. Such drugs typically demonstrate a prolonged half-life. Although the phenomenon may account for a prolonged duration of therapeutic effect, it rarely accounts for toxicity.

**(Choice E)** Drugs with a high volume of distribution (eg, amiodarone) are well distributed in the tissues and have a long half-life. These drugs may demonstrate prolonged therapeutic and/or adverse effects after discontinuation.

**Educational objective:**
Morphine generates 2 major metabolites that are metabolically active and renally cleared. These metabolites can accumulate in the bloodstream of patients with renal dysfunction and lead to opioid toxicity, evidenced by miosis, respiratory depression, and CNS depression.

**Morphine** stimulates mu opioid receptors to provide the desired effect of analgesia, but in doing so can also precipitate many undesired effects. This patient has multiple signs of **opioid toxicity**, including miosis (ie, pinpoint pupils), **respiratory depression** (evidenced by slow respiratory rate and respiratory acidosis), and CNS depression (eg, **somnolence**, coma). Morphine is primarily metabolized by the liver via glucuronidation to form **2 major metabolites**. These metabolites, morphine-3-glucoronide and **morphine-6-glucoronide**, then undergo **renal elimination** via excretion in the urine. Because the metabolites are metabolically active, **renal dysfunction** can lead to **metabolite accumulation** and opioid toxicity. Morphine-6-glucoronide is particularly responsible for toxicity, acting as a more potent mu opioid receptor agonist than morphine itself.

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**(Choice E)** Drugs with a high volume of distribution (eg, amiodarone) are well distributed in the tissues and have a long half-life. These drugs may demonstrate prolonged therapeutic and/or adverse effects after discontinuation.

**Educational objective:**

A 48-year-old woman with metastatic cervical cancer is brought to the emergency department due to worsening lethargy for the past several days. A year ago, the patient was diagnosed with cervical cancer, which has progressed despite chemotherapy treatment and metastasized to the liver and lungs. She has also developed bilateral hydronephrosis and renal failure due to ureteral compression by the tumor. The patient is receiving palliative care, and her pain has been adequately controlled with a stable dose of oral morphine. Temperature is 36.7 C (98 F), blood pressure is 110/62 mm Hg, pulse is 92/min, and respirations are 10/min. On physical examination, the patient is somnolent and responds to painful stimuli only. The pupils are small and sluggish to react. The lungs are clear to auscultation, and heart sounds are normal. The abdomen is soft and nondistended. Arterial blood gas analysis shows respiratory acidosis. Which of the following medication-related events most likely precipitated her current condition?

- A. Decreased first-pass metabolism (12%)
- ✗ B. Decreased hepatic metabolism (26%)
- C. Increased enterohepatic circulation (2%)
- ✓ D. Increased metabolite accumulation (53%)
- E. Increased volume of distribution (5%)

Incorrect
Correct answer
D

53%
Answered correctly

05 secs
Time Spent

2023
Version

Explanation

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- A. Decreased first-pass metabolism
- B. Decreased hepatic metabolism
- C. Increased enterohepatic circulation
- D. Increased metabolite accumulation
- E. Increased volume of distribution

Submit

## Explanation

Optimal antibiotic therapy often requires monitoring of serum drug concentrations to ensure adequate dosing, which is necessary to achieve therapeutic levels while avoiding toxicity (eg, nephrotoxicity due to aminoglycosides). The highest level (peak) of drug concentration is usually ½ hour after intravenous or 1 hour after intramuscular dosing, whereas the lowest drug concentration (trough) occurs during the last ½ hour before the next dose.

The **drug concentration** (mg/L) can be calculated by dividing the **drug dose** (mg) by the **volume of distribution** ($V_D$). $V_D$ refers to the theoretically required volume (in liters) if the drug were contained completely in the plasma. It can vary depending on how well the drug distributes into tissues; the higher the $V_D$, the greater the drug binds to the tissues. When drug metabolism occurs via first-order kinetics, the **half-life** ($t_{1/2}$) represents the amount of time required to lower the drug concentration by **50%**.

In this example, the first dose of the drug is 240 mg, $V_D$ is 30 L, and $t_{1/2}$ is 4 hours. The initial drug concentration is the dose (240 mg) divided by the $V_D$ (30 L), which equals 8 mg/L. After the first half-life (4 hours), the drug concentration will decrease by half to 4 mg/L. After the next half-life (4 hours later, or 8 hours after the initial dose), the drug concentration will decrease by half again to 2 mg/L **(Choices A, B, C, and E)**.

**Educational objective:**
The half-life ($t_{1/2}$) of a drug is the time required to lower its concentration by 50%. The volume of distribution ($V_D$) refers to how well the drug distributes into tissues compared to plasma; the higher the $V_D$, the greater the drug distribution into the tissues. The drug concentration (mg/L) is equal to drug dose (mg) divided by $V_D$ (L).

| Pharmacology | Pharmacology (General Principles) | Serum drug levels and half-life |
|---|---|---|
| Subject | System | Topic |

A 64-year-old man is evaluated for persistent fever and weakness. He has a history of aortic valve replacement for aortic stenosis. Physical examination reveals a new cardiac murmur with scattered petechiae and splinter hemorrhages seen on his extremities. Echocardiogram shows a vegetation involving one of the aortic valve leaflets, and blood cultures grow enterococci. As part of the patient's treatment, 240 mg of intravenous gentamicin is started. The pharmacy calculates that, in this patient, gentamicin has a volume of distribution of 30 L, a half-life of 4 hours, and demonstrates first-order and one-compartment kinetics. Which of the following is the most likely serum drug concentration just before the next dose 8 hours later?

- A. 0.5 mg/L (4%)
- ✗ B. 1 mg/L (4%)
- C. 1.5 mg/L (10%)
- ✓ D. 2 mg/L (75%)
- E. 3 mg/L (4%)

Incorrect
Correct answer
D

75%
Answered correctly

04 secs
Time Spent

2023
Version

## Explanation

Optimal antibiotic therapy often requires monitoring of serum drug concentrations to ensure adequate dosing, which is necessary to achieve therapeutic levels while avoiding toxicity (eg, nephrotoxicity due to aminoglycosides). The highest level (peak) of drug concentration is usually ½ hour after intravenous or 1 hour after intramuscular dosing, whereas the lowest drug concentration (trough) occurs during the last ½ hour before the next dose.

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- B. 1 mg/L
- C. 1.5 mg/L
- D. 2 mg/L
- E. 3 mg/L

Submit

distribution of TTE. It is eliminated by first-order kinetics and has a half-life of 10 hours. If given by a continuous infusion, approximately how much time would it require for the drug to achieve a 95% plasma steady state concentration?

- A. 10 hours (7%)
- ✗ B. 20 hours (11%)
- C. 30 hours (13%)
- ✓ D. 40 hours (67%)

Incorrect
Correct answer
D

67%
Answered correctly

03 secs
Time Spent

2023
Version

## Explanation

During continuous infusion of a drug metabolized by first-order kinetics (i.e. a constant fraction of the drug is eliminated per unit time), the steady state concentration is reached in 4 to 5 half-lives. Thus, it would take approximately 40 hours, or four times the half-life of 10 hours, for the drug in question to reach approximately 95% steady-state concentration.

**Educational objective:**
During continuous infusion of a drug metabolized by first-order kinetics, the steady state concentration is reached in 4 to 5 half-lives.

| Pharmacology | Pharmacology (General Principles) | Serum drug levels and half-life |
|---|---|---|
| Subject | System | Topic |

A new antibiotic developed for the treatment of infections caused by resistant gram-positive cocci has a volume of distribution of 11L. It is eliminated by first-order kinetics and has a half-life of 10 hours. If given by a continuous infusion, approximately how much time would it require for the drug to achieve a 95% plasma steady state concentration?

- A. 10 hours (7%)
- ✗ B. 20 hours (11%)
- C. 30 hours (13%)
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Incorrect
Correct answer
D

67%
Answered correctly

03 secs
Time Spent

2023
Version

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A new antibiotic developed for the treatment of infections caused by resistant gram-positive cocci has a volume of distribution of 11L. It is eliminated by first-order kinetics and has a half-life of 10 hours. If given by a continuous infusion, approximately how much time would it require for the drug to achieve a 95% plasma steady state concentration?

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- B. 20 hours
- C. 30 hours
- D. 40 hours

Submit

**drug interaction**. In this case, it is likely that the new **iron supplement** is interacting with tetracycline to cause **decreased absorption** of the antibiotic.

**Tetracyclines** interact with **polyvalent cations** to form **nonabsorbable chelate complexes** in the gastrointestinal tract. This effect is prominently seen with iron and is also common with other polyvalent metals (eg, aluminum, calcium, magnesium) found in widely used over-the-counter preparations (eg, antacids). Other drugs susceptible to chelation include fluoroquinolones and thyroxine.

The extent of chelation is influenced by gastric pH; the introduction of medications that raise gastric pH (eg, H2-blockers [eg, famotidine], proton pump inhibitors [eg, omeprazole]) can sometimes lead to increased chelation and loss of drug effect. Chelation can often be avoided by taking the medications at different times of the day.

**(Choice A)** Combination oral contraceptives suppress androgenic activity and reduce production of sebum. This typically leads to improvement, rather than worsening, of acne.

**(Choice B)** Clinically significant resistance to tetracyclines is uncommon in acne and unlikely to occur abruptly. In addition, besides antimicrobial effects, tetracyclines have anti-inflammatory effects in acne that would likely provide residual benefit.

**(Choice D)** Tetracyclines such as doxycycline and tigecycline are eliminated by hepatic excretion. Neither iron nor oral contraceptives would increase drug elimination.

**(Choice E)** Estrogens increase the synthesis of sex hormone–binding globulin, which can affect plasma levels of certain steroid hormones and related agents (eg, danazol, levonorgestrel). Tetracyclines are not significantly affected.

**Educational objective:**
Tetracyclines interact with polyvalent cations (eg, iron, calcium, aluminum, magnesium) to form nonabsorbable chelate complexes in the gastrointestinal tract. This can lead to significantly decreased drug absorption and therapeutic effect. Fluoroquinolones and thyroxine are also susceptible to chelation.

| Chelation drug interactions | |
|---|---|
| **Mechanism** | • Formation of insoluble compounds with polyvalent cations in the gastrointestinal tract<br>• Decreased absorption of drug |
| **Commonly involved drugs** | • Tetracyclines<br>• Fluoroquinolones<br>• Levothyroxine |
| **Chelation cations** | • Iron<br>• Calcium<br>• Magnesium<br>• Aluminum |

This young patient with acne had a good initial response to tetracycline (eg, doxycycline) therapy. However, after the initiation of new medications, she experienced a significant loss of effectiveness, suggesting a possible **drug-drug interaction**. In this case, it is likely that the new **iron supplement** is interacting with tetracycline to cause **decreased absorption** of the antibiotic.

**Tetracyclines** interact with **polyvalent cations** to form **nonabsorbable chelate complexes** in the gastrointestinal tract. This effect is prominently seen with iron and is also common with other polyvalent metals (eg, aluminum, calcium, magnesium) found in widely used over-the-counter preparations (eg, antacids). Other drugs susceptible to chelation include fluoroquinolones and thyroxine.

The extent of chelation is influenced by gastric pH; the introduction of medications that raise gastric pH (eg, H2-blockers [eg, famotidine], proton pump inhibitors [eg, omeprazole]) can sometimes lead to increased chelation and loss of drug effect. Chelation can often be avoided by taking the medications at different times of the day.

A 17-year-old girl comes to the office due to worsening acne. The patient's acne had been well controlled with oral doxycycline therapy. However, over the past month, the acne has worsened on her face and back. The patient was recently diagnosed with iron deficiency anemia due to abnormal uterine bleeding and began taking a combined oral contraceptive and an iron supplement. Physical examination shows comedones and pustules on her face and upper back. The remainder of the examination shows no abnormalities. Which of the following is the most likely cause of this patient's worsening symptoms?

- A. Adverse effect of the hormonal therapy (26%)
- ✗ B. Bacterial resistance to the antibiotic (4%)
- ✓ C. Decreased absorption of the antibiotic (48%)
- D. Increased clearance of the antibiotic (11%)
- E. Increased protein binding of the antibiotic (9%)

Incorrect
Correct answer
C

48%
Answered correctly

03 secs
Time Spent

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Explanation

| Chelation drug interactions | |
|---|---|
| **Mechanism** | • Formation of insoluble compounds with polyvalent cations in the gastrointestinal tract<br>• Decreased absorption of drug |

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Submit

The question has asked how the curve for bethanechol **(Curve A)** would be affected by the introduction of a reversible competitive antagonist. A reversible competitive antagonist is expected to require higher doses of the full agonist (bethanechol) to be present to achieve the same effect at each point along the curve. If enough of the original substrate is added, the reaction can still reach the same maximum effect. Thus, the log dose-response curve for a full agonist combined with a reversible competitive antagonist will exhibit a parallel shift to the right in the log-dose response curve, with an increase in the $ED_{50}$ and no change in the maximum effect ($E_{max}$).

**(Choice A)** Curve A is the dose-response curve for the original agonist drug in the absence of modifiers such as antagonists.

**(Choices B and C)** Both Curves B and C represent the effect of adding a noncompetitive antagonist to the agonist. Note that the $ED_{50}$ is unchanged (i.e. the $ED_{50}$ for Curves A, B and C occur at the exact same log drug concentration). This is a distinguishing characteristic of noncompetitive antagonism. The maximum effect ($E_{max}$) of Curves B and C are reduced because the noncompetitive antagonist has effectively reduced the number of receptors available for binding. The decrease in $E_{max}$ will depend on the dose of noncompetitive antagonist present and is illustrated by the difference between Curves B and C, where a higher concentration of antagonist is present in Curve C than in Curve B.

**(Choice D)** Curve D illustrates a rightward shift in the dose-response relationship, but the shift is not a parallel shift because the shape of the curve differs from that of Curve A, with changes in both $E_{max}$ and $ED_{50}$. This curve is not characteristic of any single antagonist effect and may be the result of adding multiple types of antagonists.

**Educational Objective:**
The changes in the log dose-response curve expected for the effect of a reversible competitive antagonist added to a full agonist are: 1) a parallel shift to the right in the log-dose response curve, illustrating an increase in the $ED_{50}$, and 2) no change in the maximum effect ($E_{max}$).

* Competitive=change $ED_{50}$=shift right; noncompetitive=change $E_{max}$=shift down.

Antagonists are agents that bind to but do not activate receptors. Antagonists can be either competitive or noncompetitive. Competitive antagonists bind to the exact same receptor binding sites as endogenous or exogenous agonists, thereby preventing agonist binding and activation of the receptor. Competitive antagonism can be reversible (ionic bond) or irreversible (covalent bond). The effect of a reversible competitive antagonist can be overcome by high concentrations of agonist, which cause displacement of the antagonist from the receptors by mass action.

Noncompetitive antagonists, on the other hand, bind to receptors at a site other than the primary agonist binding site, thereby causing a conformational (allosteric) change in the receptor protein that modifies the agonist binding site and prevents agonist binding. By binding to a different site than the agonist, noncompetitive antagonists are able to remain bound to the receptor even when high concentrations of agonist are present because the agonist is unable to displace noncompetitive antagonists from the receptor.

The question has asked how the curve for bethanechol **(Curve A)** would be affected by the introduction of a reversible competitive antagonist. A reversible competitive antagonist is expected to require higher doses of the full agonist (bethanechol) to be present to achieve the same effect at each point along the curve. If enough of the original substrate is added, the reaction can still reach the same maximum effect. Thus, the log dose-response curve for a full agonist combined with a reversible competitive antagonist will exhibit a parallel shift to the right in the log-dose response curve, with an increase in the $ED_{50}$ and no change in the maximum effect ($E_{max}$).

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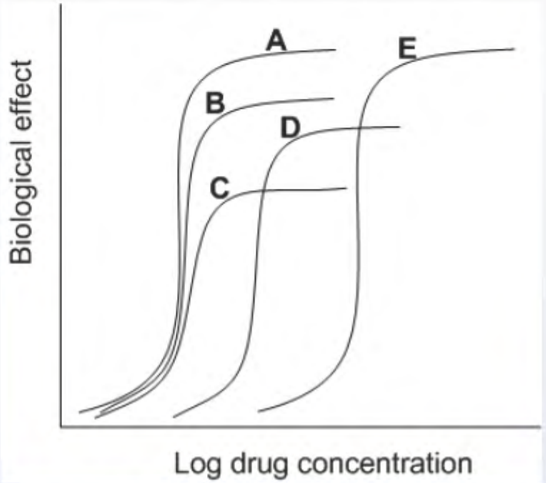
A group of investigators examined the effects of different muscarinic agonists and antagonists on the bladder musculature. The curves presented below were constructed after application of different agents. Curve A represents the effect of bethanechol, a pure cholinergic agonist.




Which of the curves most likely represents the effect of bethanechol after application of a reversible competitive antagonist?

- A. Curve A (0%)
- ✗ B. Curve B (3%)
- C. Curve C (9%)
- D. Curve D (5%)
- ✓ E. Curve E (80%)

Incorrect
Correct answer

80%
09 secs
2023

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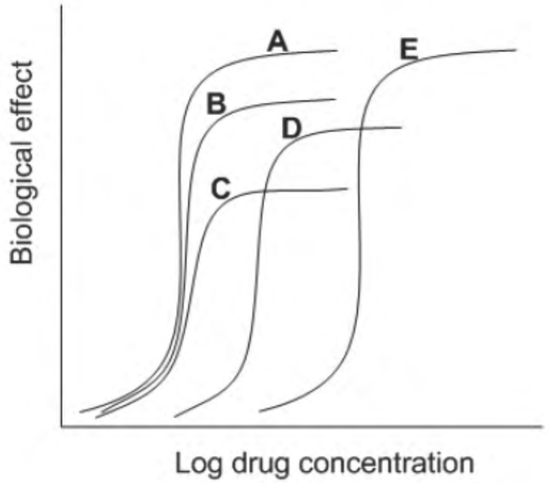


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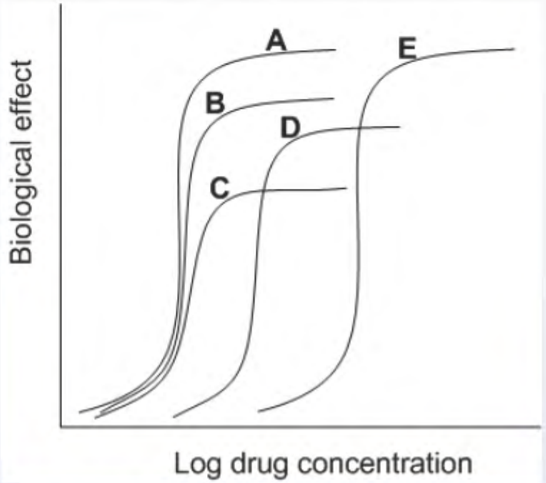


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- A. Curve A
- B. Curve B
- C. Curve C
- D. Curve D
- E. Curve E

Submit

Although commonly described as H1 receptor antagonists, antihistamines are actually inverse agonists that stabilize the receptor in the inactive state. H1 receptors are found in the vascular endothelium and bronchial smooth muscle, where they mediate vascular permeability and bronchoconstriction, as well as in the central nervous system where they are involved in alertness. Antihistaminic effects relieve nasal congestion, rhinorrhea, sneezing, and itching. First-generation antihistamines cross the blood-brain barrier and cause sedation. By contrast, second-generation antihistamines (eg, loratadine) are more specific to the histamine H1 receptor and have less permeability through the blood-brain barrier; they are generally less effective than first-generation antihistamines but have significantly fewer side effects.

**(Choice A)** Flushing and mydriasis are due to antagonism of the cholinergic receptor, not the H1 receptor.

**(Choice B)** H2 receptors are found on parietal cells in the gastric mucosa. H2 antagonists block gastric acid secretion by parietal cells.

**(Choice D)** Nicotinic cholinergic receptors are found in sympathetic and parasympathetic ganglia and on skeletal muscle cells at the neuromuscular junction. Nicotinic receptor antagonists (eg, rocuronium) are used to induce paralysis in preparation for surgery or endotracheal intubation. Adverse effects include hemodynamic instability (eg, hypotension) and respiratory insufficiency.

**(Choice E)** Alpha-1 adrenoreceptors are located on smooth muscle and neurons. Activation of these receptors increases smooth muscle tone of the iris dilator (causing mydriasis) and blood vessels (causing vasoconstriction); alpha-1 adrenergic agonists (eg, phenylephrine, oxymetazoline) can be used in patients with allergic rhinitis because their vasoconstrictive action reduces nasal congestion. However, vasoconstriction inhibits flushing.

**Educational objective:**
First-generation antihistamines are nonspecific and interact with multiple receptors, including the muscarinic receptor. This leads to anticholinergic effects (eg, fever, flushing, mydriasis, urinary retention, tachycardia, altered mental status).

This patient is likely taking a **first-generation antihistamine** (eg, diphenhydramine), which are commonly used for treating environmental allergies and mast cell-related disorders. First-generation antihistamines are nonspecific and act as **antagonists** to multiple receptors, including the **muscarinic acetylcholine receptor**. This leads to **anticholinergic** effects (eg, fever, urinary retention, decreased sweating, altered mental status). In this patient, the flushing is likely a compensatory response to dissipate excess body heat due to decreased sweating, and the pupillary dilation is due to inhibition of the iris sphincter.

Although commonly described as H1 receptor antagonists, antihistamines are actually inverse agonists that stabilize the receptor in the inactive state. H1 receptors are found in the vascular endothelium and bronchial smooth muscle, where they mediate vascular permeability and bronchoconstriction, as well as in the central nervous system where they are involved in alertness. Antihistaminic effects relieve nasal congestion, rhinorrhea, sneezing, and itching. First-generation antihistamines cross the blood-brain barrier and cause sedation. By contrast, second-generation antihistamines (eg, loratadine) are more specific to the histamine H1 receptor and have less permeability through the blood-brain barrier; they are generally less effective than first-generation antihistamines but have significantly fewer side effects.

**(Choice A)** Flushing and mydriasis are due to antagonism of the cholinergic receptor, not the H1 receptor.

**(Choice B)** H2 receptors are found on parietal cells in the gastric mucosa. H2 antagonists block gastric acid secretion by parietal cells.

**(Choice D)** Nicotinic cholinergic receptors are found in sympathetic and parasympathetic ganglia and on skeletal muscle cells at the neuromuscular junction. Nicotinic receptor antagonists (eg, rocuronium) are used to induce paralysis in preparation for surgery or endotracheal intubation. Adverse effects include hemodynamic instability (eg, hypotension) and respiratory insufficiency.

**(Choice E)** Alpha-1 adrenoreceptors are located on smooth muscle and neurons. Activation of these receptors increases smooth muscle tone of the iris dilator (causing mydriasis) and blood vessels (causing vasoconstriction);

**Anticholinergic toxicity**

| Symptom | Mechanism |
|---|---|
| **"Hot as a hare"**<br>↑ Body temperature | • ↓ Sweating leads to ↓ heat dissipation |
| **"Dry as a bone"**<br>↓ Secretions (eg, mucous membranes, sweat glands) | • ↓ Glandular secretion & smooth muscle contraction |
| **"Red as a beet"**<br>Flushed skin | • Superficial vasodilation from ↑ body heat |
| **"Blind as a bat"**<br>Cycloplegia, mydriasis | • Paralysis of ciliary muscle & iris sphincter |
| **"Mad as a hatter"**<br>Altered mental status | • Permeates blood-brain barrier & affects CNS pathways |
| **"Full as a flask"**<br>Constipation, urinary retention | • ↓ Intestinal smooth muscle contraction<br>• ↓ Detrusor contraction & ↓ internal urethral sphincter relaxation |
| **"Fast as a fiddle"**<br>Tachycardia | • ↓ Vagal tone at the sinoatrial node |

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| Anticholinergic toxicity | |
|---|---|
| **Symptom** | **Mechanism** |
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A 52-year-old man comes to the office for an annual preventive visit. He has a history of seasonal allergies, and has recently started taking a medication that has improved his runny nose, sneezing, and watery eyes. Medical history is remarkable for diet-controlled type 2 diabetes mellitus and eczema. He is not on any other medications. He does not use tobacco, alcohol, or illicit drugs. Examination shows a well-appearing man with flushed cheeks and dilated pupils. This patient's physical examination findings are best explained by which of the following mechanisms?

- A. Antagonism of H1 receptors (18%)
- ✗ B. Antagonism of H2 receptors (4%)
- ✓ C. Antagonism of muscarinic receptors (57%)
- D. Antagonism of nicotinic receptors (1%)
- E. Stimulation of alpha-1 adrenoreceptors (17%)

Incorrect
Correct answer
C

57%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

| Anticholinergic toxicity | |
|---|---|
| **Symptom** | **Mechanism** |
| **"Hot as a hare"**<br>↑ Body temperature | • ↓ Sweating leads to ↓ heat dissipation |

A 52-year-old man comes to the office for an annual preventive visit. He has a history of seasonal allergies, and has recently started taking a medication that has improved his runny nose, sneezing, and watery eyes. Medical history is remarkable for diet-controlled type 2 diabetes mellitus and eczema. He is not on any other medications. He does not use tobacco, alcohol, or illicit drugs. Examination shows a well-appearing man with flushed cheeks and dilated pupils. This patient's physical examination findings are best explained by which of the following mechanisms?

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- C. Antagonism of muscarinic receptors
- D. Antagonism of nicotinic receptors
- E. Stimulation of alpha-1 adrenoreceptors

Submit

| | |
|---|---|
| Cyclophosphamide | Ritonavir (protease inhibitors) |

This patient has suffered a **thromboembolic stroke**, likely the result of a dislodged left atrial thrombus that formed due to an adverse drug interaction leading to **inadequate anticoagulation**. Many substances cause induction or inhibition of cytochrome P450 (CYP450) hepatic microsomal enzymes, which are responsible for the majority of drug metabolism. CYP450 interactions should be considered when selecting and dosing medications, as changes in enzyme activity affect the rate of drug metabolism.

Alterations in plasma drug levels are especially important when considering medications that are vital to a patient's health or have a high propensity for toxicity, such as warfarin. For example, **warfarin** can interact with **St John's wort**, an over-the-counter medicinal herb known for both its anti-inflammatory and antidepressant properties. St John's wort **induces hepatic CYP450 enzymes**, resulting in increased warfarin metabolism, decreased drug levels, and inadequate anticoagulation.

**(Choices A, B, C, D, and E)** These drugs are known to inhibit CYP450 enzymes and increase warfarin levels, leading to an increased risk of bleeding complications.

**(Choice F)** Oral penicillin V and warfarin do not have any significant interactions. Antibiotics in general reduce the intestinal bacterial load, which reduces vitamin K synthesis and could potentiate warfarin's anticoagulant effects.

**Educational objective:**
St John's wort induces cytochrome P450 hepatic microsomal enzymes. As a result, a wide variety of drugs that are metabolized by these enzymes, such as warfarin, will have lower plasma concentrations and decreased efficacy.

**References**

- Effect of St John's wort and ginseng on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects.

Pharmacology  Pharmacology (General Principles)  Anticoagulants

| Cytochrome P450 (CYP450) interactions | |
|---|---|
| **Inducers** | **Inhibitors** |
| Carbamazepine | Amiodarone |
| Barbiturates | Cimetidine |
| Phenytoin | Fluoroquinolones |
| Rifampin | Clarithromycin |
| Griseofulvin | Azole antifungals |
| St. John's wort | Grapefruit juice |
| Modafinil | Isoniazid |
| Cyclophosphamide | Ritonavir (protease inhibitors) |

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A 65-year-old man is brought to the emergency department after developing sudden-onset right-side weakness and difficulty speaking. He has a history of paroxysmal atrial fibrillation and has been taking warfarin for the past several years with a stable prothrombin time. His wife adds that he started taking a new drug 2 weeks ago, but she does not remember its name. Physical examination shows right hemiplegia, right hemisensory loss, expressive aphasia, and right homonymous hemianopia. MRI of the head shows a left middle cerebral artery territory infarct. Transesophageal echocardiogram reveals a small thrombus in the left atrium. This patient most likely started taking which of the following drugs recently?

- A. Amiodarone (10%)
- ✗ B. Cimetidine (14%)
- C. Ciprofloxacin (3%)
- D. Clarithromycin (3%)
- E. Fluconazole (4%)
- F. Penicillin V (0%)
- ✓ G. St John's wort (61%)

Incorrect
Correct answer
G

61%
Answered correctly

03 secs
Time Spent

2023
Version

Explanation

**Cytochrome P450 (CYP450) interactions**

A 65-year-old man is brought to the emergency department after developing sudden-onset right-side weakness and difficulty speaking. He has a history of paroxysmal atrial fibrillation and has been taking warfarin for the past several years with a stable prothrombin time. His wife adds that he started taking a new drug 2 weeks ago, but she does not remember its name. Physical examination shows right hemiplegia, right hemisensory loss, expressive aphasia, and right homonymous hemianopia. MRI of the head shows a left middle cerebral artery territory infarct. Transesophageal echocardiogram reveals a small thrombus in the left atrium. This patient most likely started taking which of the following drugs recently?

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- D. Clarithromycin
- E. Fluconazole
- F. Penicillin V
- G. St John's wort

Submit

transporter:

- In the intestine, apical P-gp transporters pump digoxin molecules back into the intestinal lumen, reducing total absorption and bioavailability; inhibition of these transporters **increases digoxin absorption** and bioavailability.
- In the renal tubules, apical P-gp transporters pump digoxin molecules into the urine to facilitate digoxin excretion; inhibition of these transporters **decreases digoxin excretion**.

P-gp transporters are also important in chemotherapy administration, as some tumor cells use the efflux pumps as a mechanism of chemotherapy resistance.

**(Choice A)** Blockade of a biliary transport protein can decrease enterohepatic recirculation (ie, intestinal reabsorption of a drug after initial metabolism by the liver), reducing blood levels and necessitating a dose increase (eg, cyclosporine has this effect on mycophenolate). Digoxin does not undergo substantial enterohepatic recirculation.

**(Choice B)** Inhibition, rather than induction, of cytochrome P-450 can increase the blood levels of some drugs and necessitate a dose reduction. Amiodarone is an inhibitor of cytochrome P-450, but digoxin is not hepatically cleared and its blood levels are not affected by cytochrome P-450 inhibition.

**(Choice D)** Proton pump inhibitors slightly increase digoxin absorption by reducing gastric acid production and increasing gastric pH; however, amiodarone has no effect on gastric acid production.

**(Choice E)** Amiodarone slightly inhibits (rather than induces) the $Na^+/K^+$-ATPase in cardiomyocytes, but this additive effect with digoxin is not enough to warrant decreasing the dose (the effect of P-gp inhibition is far greater).

**Educational objective**:
Amiodarone increases digoxin blood levels via inhibition of P-glycoprotein transmembrane efflux transporters in the intestine to cause increased digoxin absorption, and in the kidneys to cause decreased digoxin excretion. Therefore, a dose reduction of digoxin is needed when it is coadministered with amiodarone.

**Digoxin** inhibits the $Na^+/K^+$-ATPase in cardiomyocytes to increase cardiac contractility, making it useful in some patients with heart failure with reduced ejection fraction. Oral digoxin is absorbed by the gastrointestinal tract with a bioavailability of approximately 70% and once in the bloodstream is mostly **renally cleared**. The drug has a **narrow therapeutic index** and can be dangerous in toxicity; therefore, careful dosing adjustments must be made when absorption and/or clearance is altered.

**Amiodarone**, an antiarrhythmic drug that may be used in the management of atrial fibrillation, **increases digoxin blood levels** by stimulating both increased intestinal absorption and reduced renal clearance of the drug. These effects are both mediated by amiodarone's **inhibition of the P-glycoprotein** (P-gp) transmembrane efflux transporter:

- In the intestine, apical P-gp transporters pump digoxin molecules back into the intestinal lumen, reducing total absorption and bioavailability; inhibition of these transporters **increases digoxin absorption** and bioavailability.
- In the renal tubules, apical P-gp transporters pump digoxin molecules into the urine to facilitate digoxin excretion; inhibition of these transporters **decreases digoxin excretion**.

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A 79-year-old man is admitted to the hospital due to worsening dyspnea. He has a history of paroxysmal atrial fibrillation and severe heart failure with reduced ejection fraction. Physical examination shows tachycardia with an irregularly irregular rhythm, elevated jugular venous pressure, bibasilar lung crackles, and peripheral edema. ECG reveals atrial fibrillation with rapid ventricular response. After initial intravenous therapy, daily oral amiodarone is started. Due to the initiation of amiodarone, the patient's home digoxin dose is reduced by 50%. This change in dose is warranted because of which of the following effects of amiodarone?

- A. Blockade of biliary transport protein
- ✗ B. Induction of cytochrome P-450
- ✓ C. Inhibition of P-glycoprotein
- D. Reduction of gastric acid production
- E. Stimulation of Na+/K+-ATPase

Incorrect
Correct answer
C

Collecting Statistics

42 secs
Time Spent

2023
Version

## Explanation

**Digoxin** inhibits the $Na^+/K^+$-ATPase in cardiomyocytes to increase cardiac contractility, making it useful in some patients with heart failure with reduced ejection fraction. Oral digoxin is absorbed by the gastrointestinal tract with a bioavailability of approximately 70% and once in the bloodstream is mostly **renally cleared**. The drug has a **narrow therapeutic index** and can be dangerous in toxicity; therefore, careful dosing adjustments must be made when absorption and/or clearance is altered.

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Submit

This patient who recently received systemic chemotherapy for breast cancer and now has progressive hematuria and suprapubic tenderness most likely has **hemorrhagic cystitis** caused by a nitrogen mustard-based chemotherapeutic agent, such as **cyclophosphamide** or one of its analogs (eg, ifosfamide). These agents are metabolized by the kidneys into **acrolein**, which is then excreted in the urine. Acrolein is toxic to uroepithelial cells and can cause cell death and necrosis if allowed to be in contact with these cells for a prolonged period.

Hemorrhagic cystitis associated with nitrogen mustard-based chemotherapy can be **prevented** by aggressive hydration and the coadministration of **mesna** (2-mercaptoethanesulfonate), a sulfhydryl compound that binds and inactivates the toxic metabolites of the chemotherapeutic agents in the urine.

**(Choice A)** Dexrazoxane is an iron-chelating agent that can help prevent anthracycline-induced (eg, doxorubicin) cardiotoxicity.

**(Choice B)** Filgrastim is a granulocyte colony-stimulating factor (G-CSF) analog used to stimulate the proliferation and differentiation of granulocytes in patients with neutropenia, as can occur after chemotherapy. This patient is afebrile, and her urinalysis is not suggestive of a urinary tract infection.

**(Choice C)** Leucovorin, or folinic acid, is a drug used in the treatment of methotrexate overdose. It also enhances the cytotoxic action of 5-fluorouracil (5-FU) and is used in combination with 5-FU in some cases of colorectal cancer.

**(Choice E)** Ondansetron inhibits serotonin 5-$HT_3$ receptors and is used primarily to treat nausea and vomiting following chemotherapy.

**Educational objective:**
Hemorrhagic cystitis during therapy with cyclophosphamide or ifosfamide is caused by the urinary excretion of the toxic metabolite acrolein. It can be prevented by aggressive hydration, bladder irrigation, and administration of mesna, a sulfhydryl compound that binds acrolein in the urine.

Pharmacology  Pharmacology (General Principles)  Chemotherapy

A 56-year-old woman comes to the emergency department due to 3 days of frequent urination, suprapubic pain, dysuria, and progressive hematuria. She has had no fevers or chills. The patient has a history of lymph-node-positive breast cancer that was diagnosed following a routine mammogram. A month ago, she began treatment with systemic chemotherapy. Temperature is 37.1 C (98.8 F). Suprapubic tenderness is present on abdominal examination. Hemoglobin is 9.8 g/dL. Urinalysis shows numerous red blood cells but no leukocyte esterase or bacteria. Which of the following could have prevented this patient's current condition?

- A. Dexrazoxane (4%)
- B. Filgrastim (7%)
- ✗ C. Folinic acid (9%)
- ✓ D. Mesna (75%)
- E. Ondansetron (2%)

Incorrect
Correct answer
D

75%
Answered correctly

05 secs
Time Spent

2023
Version

## Explanation

This patient who recently received systemic chemotherapy for breast cancer and now has progressive hematuria and suprapubic tenderness most likely has **hemorrhagic cystitis** caused by a nitrogen mustard-based chemotherapeutic agent, such as **cyclophosphamide** or one of its analogs (eg, ifosfamide). These agents are metabolized by the kidneys into **acrolein**, which is then excreted in the urine. Acrolein is toxic to uroepithelial cells and can cause cell death and necrosis if allowed to be in contact with these cells for a prolonged period.

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- A. Dexrazoxane
- B. Filgrastim
- C. Folinic acid
- D. Mesna
- E. Ondansetron

Submit

depending on the solubility of the drug (eg, hydrophilic, hydrophobic).

**Aminoglycosides** are large, charged molecules that cannot cross cell membranes; their volume of distribution is limited to the extracellular space, which increases only marginally in obese individuals. As a result, **dosing in obese patients** is based on an **adjusted body weight** that takes into account only a portion (~40%) of the excess adipose mass.

**(Choice B)** The route of elimination does not directly impact weight-based drug dosing, aside from the fact that lipophilic drugs more often undergo hepatic elimination. Furthermore, aminoglycosides are not metabolized by the liver; they are freely filtered by the glomerulus and excreted unchanged in the urine.

**(Choice C)** The vast majority of drugs, including aminoglycosides, undergo first- (not zero-) order metabolism. In addition, body weight adjustments with regard to medication dosing are usually made according to the way a drug distributes within the body's tissues.

**(Choice D)** Acidic drugs with a high degree of plasma protein binding (eg, warfarin) are retained in the intravascular space and have a limited volume of distribution that is less affected by body weight. In contrast, aminoglycosides have minimal plasma protein binding and can distribute extensively into the interstitial compartment.

**(Choice E)** Lipophilic drugs partition extensively into adipose tissues; their volume of distribution is better correlated with total body weight than with lean or adjusted body weight. Highly lipophilic drugs (eg, phenytoin) are tightly sequestered within adipose tissue and often require an initial loading dose to saturate fat stores and achieve adequate serum levels.

**Educational objective:**
Many drugs are dosed based on total body weight to improve safety and efficacy. In obese individuals, use of lean body weight or an adjusted body weight may be necessary when dosing hydrophilic drugs (eg, aminoglycosides) that do not distribute into adipose tissue.

**References**

Drugs are typically dosed to maintain plasma drug concentrations within a target range. Although fixed drug dosing is convenient for providers and patients, dosing based on **body weight** (eg, mg/kg) is often used to improve safety and efficacy, particularly for medications with a narrow therapeutic window (eg, heparins, aminoglycosides, anesthetics).

Body weight affects both the rate of drug clearance and the volume of distribution. Drug clearance rates correlate closely with lean body weight (ie, the weight of all nonadipose tissues, including muscle, liver, kidneys). Likewise, the volume of distribution for most drugs also gets larger as lean body mass increases. However, **obesity** causes a **disproportional increase in adipose mass**, which can have a variable effect on the volume of distribution depending on the solubility of the drug (eg, hydrophilic, hydrophobic).

**Aminoglycosides** are large, charged molecules that cannot cross cell membranes; their volume of distribution is limited to the extracellular space, which increases only marginally in obese individuals. As a result, **dosing in obese patients** is based on an **adjusted body weight** that takes into account only a portion (~40%) of the excess adipose mass.

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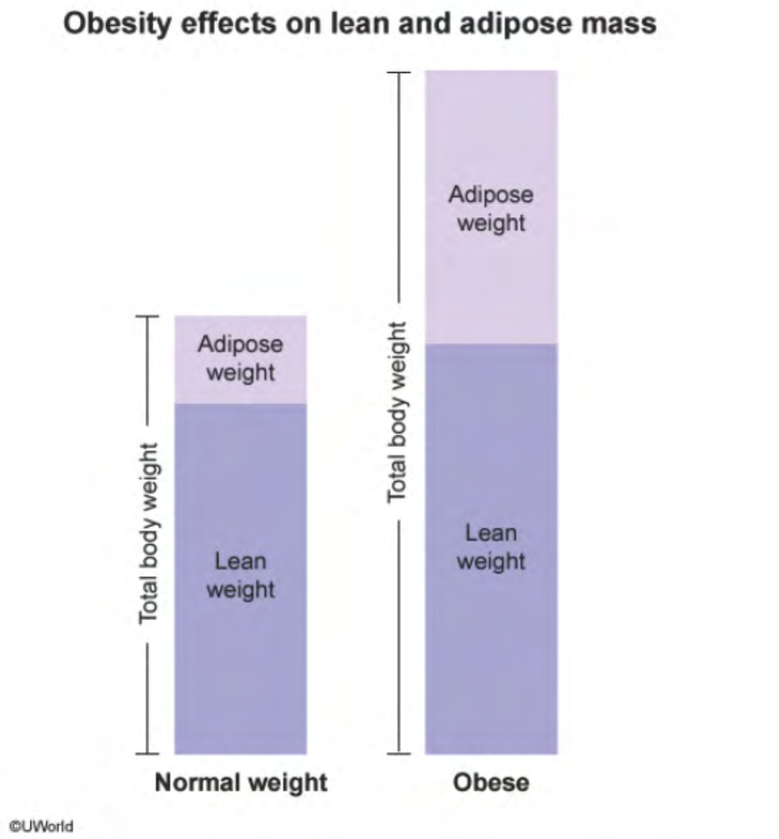


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a **disproportional increase in adipose mass**, which can have a variable effect on the volume of distribution

A 58-year-old man with type 2 diabetes mellitus comes to the emergency department with fever, malaise, lower abdominal discomfort, and left flank pain. The patient has a history of diabetic autonomic neuropathy with bladder dysfunction and has been hospitalized multiple times for recurrent urinary tract infections. His temperature is 39.4 C (103 F), blood pressure is 94/50 mm Hg, and pulse is 118/min. Height is 180 cm (5 ft 11 in), weight is 150 kg (331 lb), and BMI is 46 kg/m$^2$. On examination, there is suprapubic and left costovertebral angle tenderness. After review of culture and sensitivity tests from his prior hospitalization, the patient is started on an empiric antibiotic regimen that includes an aminoglycoside. While calculating the appropriate dosage, the hospital pharmacy uses an adjusted body weight that is lower than the patient's actual body weight. Which of the following best explains the use of this adjusted parameter?

- ✓ A. Distribution of the drug is limited to the extracellular fluid compartment (36%)
- ✗ B. Elimination of the drug is predominately by hepatic clearance (8%)
- C. Metabolism of the drug proceeds via zero-order kinetics (8%)
- D. The drug exhibits a high degree of plasma protein binding (21%)
- E. The drug is tightly sequestered within adipose tissues (24%)

Incorrect
Correct answer
A

36%
Answered correctly

04 secs
Time Spent

2023
Version

Explanation

**Obesity effects on lean and adipose mass**

A 58-year-old man with type 2 diabetes mellitus comes to the emergency department with fever, malaise, lower abdominal discomfort, and left flank pain. The patient has a history of diabetic autonomic neuropathy with bladder dysfunction and has been hospitalized multiple times for recurrent urinary tract infections. His temperature is 39.4 C (103 F), blood pressure is 94/50 mm Hg, and pulse is 118/min. Height is 180 cm (5 ft 11 in), weight is 150 kg (331 lb), and BMI is 46 kg/m$^2$. On examination, there is suprapubic and left costovertebral angle tenderness. After review of culture and sensitivity tests from his prior hospitalization, the patient is started on an empiric antibiotic regimen that includes an aminoglycoside. While calculating the appropriate dosage, the hospital pharmacy uses an adjusted body weight that is lower than the patient's actual body weight. Which of the following best explains the use of this adjusted parameter?

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- B. Elimination of the drug is predominately by hepatic clearance
- C. Metabolism of the drug proceeds via zero-order kinetics
- D. The drug exhibits a high degree of plasma protein binding
- E. The drug is tightly sequestered within adipose tissues

Submit

- **Clearance (CL)** represents the volume of plasma completely cleared of a substance per unit time (eg,

Exhibit Display

| Pharmacokinetic parameter | Formula | Note |
|---|---|---|
| **Half life** | $V_d \times 0.7 / CL$ | Steady-state concentration is achieved in 4-5 half-lives. |
| **Maintenance dose** | $C_{ss} \times CL \times$ dosing interval | Maintenance dose is decreased in patients with renal or hepatic impairment. |
| **Loading dose** | $V_d \times C_{ss}$ | Loading dose is affected by body weight and composition. |

**CL** = drug clearance; **Css** = steady-state plasma concentration; **Vd** = volume of distribution.

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almost completely eliminated after 5 half-life intervals. The half-life can be calculated from the drug's volume of

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| First-order drug kinetics | |
|---|---|
| **Elapsed half-lifes** | **Amount eliminated** |
| 0 | 0% |
| 1 | 50% |
| 2 | 75% |
| 3 | 87.5% |
| 4 | 93.75 |
| 5 | 96.875% |

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The half-life of a drug can be calculated using these parameters, as follows:

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The half-life of a drug can be calculated using these parameters, as follows:

the drug from the body. Increased glucuronidation or glomerular filtration would increase plasma CL of the drug, leading to decreased drug half-life **(Choices A and B)**.

- **Volume of distribution ($V_d$)** refers to the extent to which a drug distributes in body tissue compared to its plasma concentration. A drug's $V_d$ is determined by its intrinsic properties (eg, lipid solubility, protein binding), as well as patient factors such as body weight and composition (eg, increased fat vs lean mass). In general, a **higher $V_d$** means that the drug is increasingly bound to body tissues with a smaller proportion found in the plasma. Because **plasma concentrations are lower** for any given dose, drugs with higher $V_d$ take longer to eliminate from the body and therefore have a **longer half-life**.

The half-life of a drug can be calculated using these parameters, as follows:

$$t_{1/2} = (0.7 \times V_d) / CL$$

In this case, the increased drug half-life seen in certain patients is likely due to **increased total body weight**, resulting in a higher volume of distribution.

**(Choices C and D)** Oral bioavailability can vary between individuals due to intrinsic differences (eg, age, sex, disease), diet, and medications (eg, proton pump inhibitors). Although increased oral bioavailability can raise peak serum drug levels, drug half-life would not be affected because the amount of drug eliminated per unit time increases as the drug's plasma concentration increases (true of drugs exhibiting first-order kinetics, which account for the vast majority of all clinically used drugs).

**Educational objective:**
Half-life ($t_{1/2}$) is a measure of how quickly a drug with first-order kinetics is eliminated from the body. A drug is almost completely eliminated after 5 half-life intervals. The half-life can be calculated from the drug's volume of distribution ($V_d$) and clearance rate (CL) using the following equation:

$$t_{1/2} = (0.7 \times V_d) / CL.$$

The **half-life ($t_{1/2}$)** is the time required for the plasma concentration of a drug with first-order elimination kinetics to decrease by 50%. At time zero, 100% of the drug is present, and with the passage of each subsequent half-life, half of the remaining drug is eliminated. After 5 half-life intervals, a drug is almost completely eliminated from the body. A drug's half-life depends on 2 pharmacokinetic properties:

- **Clearance (CL)** represents the volume of plasma completely cleared of a substance per unit time (eg, mL/min). The CL rate is constant for most drugs and depends on the particular metabolic conversion (eg, glucuronidation to inactive form) and/or elimination pathways (eg, biliary or urinary excretion) used to remove the drug from the body. Increased glucuronidation or glomerular filtration would increase plasma CL of the drug, leading to decreased drug half-life **(Choices A and B)**.
- **Volume of distribution ($V_d$)** refers to the extent to which a drug distributes in body tissue compared to its plasma concentration. A drug's $V_d$ is determined by its intrinsic properties (eg, lipid solubility, protein binding), as well as patient factors such as body weight and composition (eg, increased fat vs lean mass). In general, a **higher $V_d$** means that the drug is increasingly bound to body tissues with a smaller proportion found in the plasma. Because **plasma concentrations are lower** for any given dose, drugs with higher $V_d$ take longer to eliminate from the body and therefore have a **longer half-life**.

The half-life of a drug can be calculated using these parameters, as follows:

$$t_{1/2} = (0.7 \times V_d) / CL$$

In this case, the increased drug half-life seen in certain patients is likely due to **increased total body weight**, resulting in a higher volume of distribution.

**(Choices C and D)** Oral bioavailability can vary between individuals due to intrinsic differences (eg, age, sex, disease), diet, and medications (eg, proton pump inhibitors). Although increased oral bioavailability can raise peak serum drug levels, drug half-life would not be affected because the amount of drug eliminated per unit time

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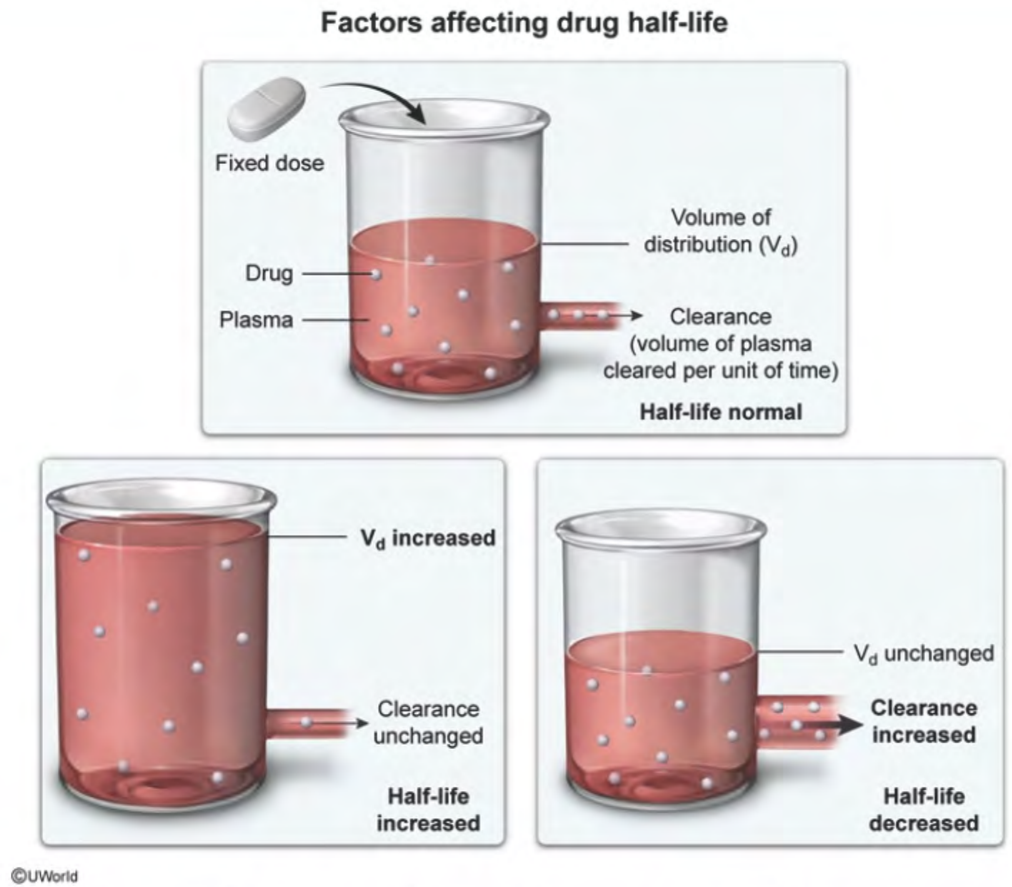


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- A. Drug glucuronidation (22%)
- ✗ B. Glomerular filtration rate (10%)
- C. Oral bioavailability (9%)
- D. Peak serum drug levels (6%)
- ✓ E. Volume of distribution (51%)

Incorrect
Correct answer
E

51%
Answered correctly

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Time Spent

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Explanation

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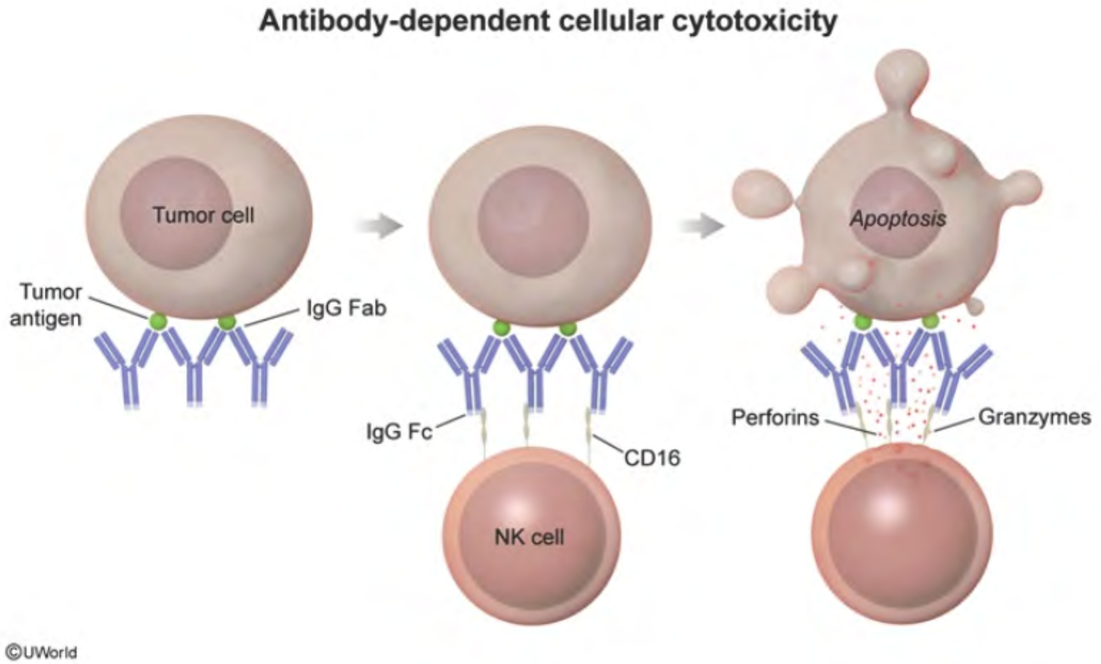


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Immunology | Pharmacology (General Principles) | Cytokines

Although patients with advanced renal cell carcinoma who undergo IL-2 therapy may enter long-lasting remission, high-dose IL-2 treatment is nonspecific and causes significant adverse effects due to excessive cytokine production (eg, capillary leak syndrome). Therefore, most patients are now treated with newer immunotherapy agents such as CTLA-4 inhibitors (eg, ipilimumab) or PD-1 protein inhibitors (eg, nivolumab) that deliver more targeted therapy and are better tolerated.

**(Choice A)** Tumor hypoxia and lactic acid production increase release of vascular endothelial growth factor (VEGF), which promotes angiogenesis required for tumor growth. Therefore, anti-VEGF immunotherapy (eg, bevacizumab) can induce a potent antitumor response; it is often used for lung and colorectal cancer.

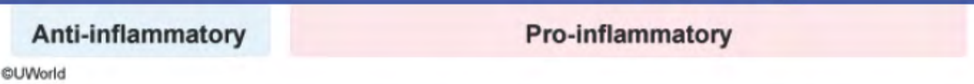
**(Choice B)** Although CD8 and NK cells induce cell death via apoptosis, this effect is not mediated by direct binding of IL-2 to the tumor cell. Certain chemotherapy drugs (eg, etoposide, vincristine, cyclophosphamide) directly induce apoptosis by damaging tumor cell DNA, the cytoskeleton, or mitochondria.

**(Choice C)** Monoclonal antibodies that target specific cell surface molecules on the tumor can induce tumor cell death via antibody-dependent cellular cytotoxicity. An example of this type of immunotherapy is alemtuzumab, a drug for chronic lymphocytic leukemia that targets a cell surface receptor (CD52) found primarily on mature lymphocytes. However, IL-2 does not directly interact with the Fc receptor on cytotoxic cells.

**(Choice E)** Although IL-2 triggers CD8 cells to increase expression of the inhibitory receptor PD-1 (programmed cell death protein 1), engagement of this receptor leads to T-cell exhaustion, not increased antitumor activity.

**Educational objective:**
Interleukin-2 (IL-2) is endogenously produced by CD4 cells, CD8 cells, and natural killer (NK) cells and has strong proinflammatory and some anti-inflammatory effects. High-dose IL-2 therapy can be used for advanced renal cell carcinoma and metastatic melanoma; this can lead to long-lasting remission due to increased cytotoxic activity of NK cells against the tumor.

Immunology  Pharmacology (General Principles)  Cytokines




**Interleukin-2** (IL-2) is a cytokine produced endogenously by **activated CD4 cells**, CD8 cells, and natural killer (NK) cells. High-dose IL-2 infusions can also be administered to patients with advanced renal cell carcinoma or metastatic melanoma in order to increase **antitumor lymphocyte activity**, as follows:

- **CD4 cells:** IL-2 converts activated CD4 cells into type 1 T-helper cells, which then secrete inflammatory cytokines (eg, IFN-gamma, TNF-alpha, IL-2) that drive an antitumor response.
- **CD8 cells:** IL-2 expands the pool of activated CD8 cells and increases their cytotoxic killing with granzymes and perforins.
- **NK cells:** IL-2 triggers proliferation of NK cells and **dramatically increases** their **cytotoxic activity**; most of the antitumor effect of IL-2 therapy comes from increased NK cell activity.

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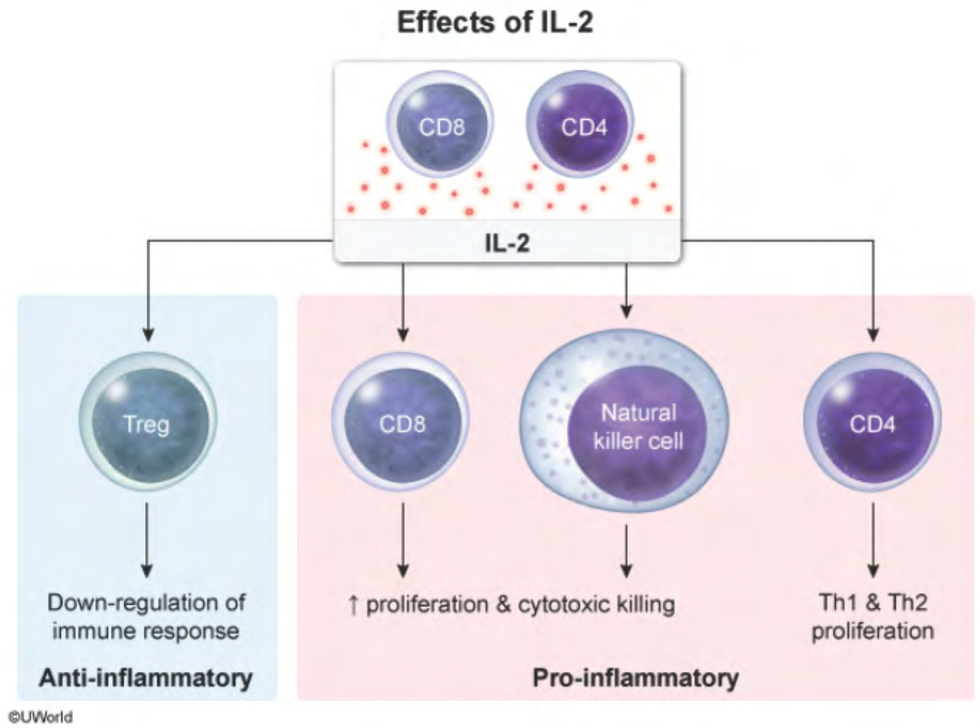


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A 63-year-old man comes to the clinic after noticing a reddish tinge to his urine. During evaluation for hematuria, an abdominal CT scan reveals a mass in his left kidney. Further work-up shows multiple lung and bone nodules. CT-guided biopsy of a peripherally located lung nodule demonstrates renal cell carcinoma. High-dose interleukin-2 (IL-2) treatment is started, and 4 weeks later there is a significant reduction in the patient's tumor burden. Which of the following mechanisms was most likely responsible for regression of this patient's malignancy?

- A. Antiangiogenic effect of IL-2 (5%)
- ✕ B. Direct damage to tumor cells by IL-2 (2%)
- C. IL-2 binding to Fc receptors on cytotoxic lymphocytes (26%)
- ✓ D. Enhanced activity of natural killer cells (46%)
- E. Increased expression of PD-1 protein on CD8 T cells (19%)

Incorrect
Correct answer
D

46%
Answered correctly

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Time Spent

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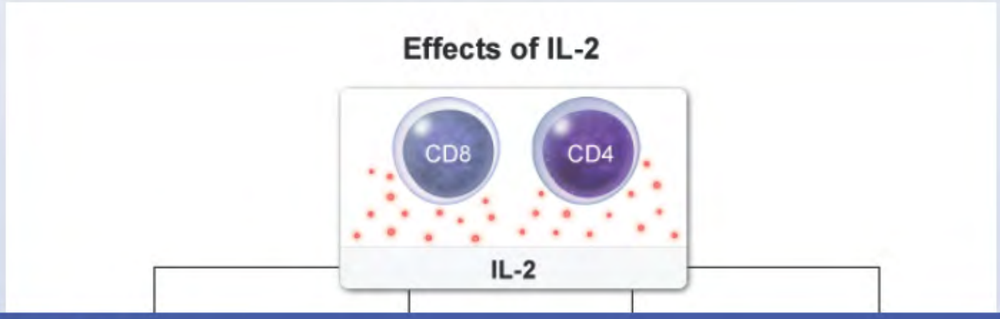
Explanation



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